Minnesota Obesity/Nutrition Research Center
Start Date: 1995
Status: Ongoing
Source of NIH Support: NIDDK
Website: www.umn.edu/mnoc

Organization and Goals

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

With the mission of prevention defined, the Minnesota ONRC has established three goals:

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

The Minnesota ONRC is primarily a research center. Thus it encourages and supports studies directed at these goals by:

- Assisting principal investigators in conducting relevant research by providing resources through the core system;
- Stimulating new interest and new collaborations in research into obesity, eating disorders, and energy metabolism;
- Supporting new research efforts in these areas related to obesity; and
- Supporting education in obesity and eating disorders in our academic and public communities.

The Minnesota ONRC incorporates 60 investigators from five institutions: the University of Minnesota, the Minneapolis VA Medical Center, the Hennepin County Medical Center, HealthPartners Research Foundation, and the Mayo Clinic in Rochester. Research interests are diverse and encompass expertise in public health, physiology of energy metabolism, adipose tissue metabolism, eating disorders and behavioral contributions to obesity, and neural regulation. The Minnesota ONRC is established under the authority of the University of Minnesota Dean's Policy Committee, with direct reporting to the Associate Dean for Research of the Medical School. A consortium arrangement exists with the Mayo Clinic for the purpose of creating the ONRC and its Metabolic Studies Core. Specific authority for oversight for the ONRC is with the Dean of the Medical School in conjunction with the Dean of the School of Public Health.

Core Laboratories

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

External Advisory Group Members:

Susan K. Fried, Ph.D., Baltimore VAMC and the School of Medicine, University of Maryland
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Basic Mechanisms Core: Cary N. Mariash, M.D., Director; Howard C. Towle, Ph.D., Co-Director

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

Eating Disorders Subcore: Scott J. Crow, M.D., Director

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

Pilot and Feasibility Studies

Effect of Brain-Derived Neurotrophin Factor (BDNF) in the Central Nervous System (CNS) on Energy Metabolism. ChuanFeng Wang, M.D., Ph.D., Research Service, VA Medical Center, Minneapolis, MN. BDNF is a neurotrophin that plays important roles in differentiation, survival, and plasticity of the CNS. BDNF mRNA and protein are heavily distributed in the hypothalamus, limbic system, and other areas. Its tyrosine kinase receptor, Trk B, is also widely spread throughout the CNS. Recent studies show that BDNF decreases feeding and body weight after injection into the ventricles. Systemic injection increases body temperature and oxygen consumption, and BDNF (+/-) heterozygous animals, which have low BDNF gene expression in specific hypothalamic sites, are obese. Together these data suggest that BDNF may play an important role in energy balance. However, specific sites of BDNF action and short term BDNF effects have not yet been reported. A full understanding of CNS BDNF effects on energy balance is necessary. In our preliminary study targeting the paraventricular nucleus of hypothalamus (PVN), a single injection of BDNF significantly decreased feeding and body weight gain for up to 48 hours, suggesting that BDNF may regulate energy balance in specific sites that are important to energy metabolism. To test the hypothesis that BDNF in the CNS decreases energy intake and

increases the capacity for thermogenesis, the proposed studies will determine: 1) specific brain sites of action for BDNF (via injecting BDNF with different doses into specific sites in food deprived rats and measuring food intake and body weight change); 2) non-aversive doses of BDNF that inhibit feeding (by measuring saccharin solution intake in a conditioned taste aversion paradigm); 3) influence of BDNF on capacity for thermogenesis (via measuring uncoupling protein gene expression in peripheral tissues) and other metabolic factors (via measuring leptin and free fatty acid levels); and 4) functional interactions between BDNF and other energy regulatory neuropeptide systems (via co-injecting BDNF and other neuropeptides and measuring food intake and body weight change, and via measuring neuropeptide mRNA and protein levels in specific brain sites after BDNF treatment). The proposed studies will address the role of BDNF in energy balance regulation and will provide information important to the prevention and treatment of obesity. This activity led to the successful award of a Department of Veterans Affairs/Merit Review Entry Proposal grant.

The Effects of Aerobic Exercise on Vascular Structure and Function in Obese Children. Daniel R. Kaiser, Ph.D., Cardiovascular Division, University of Minnesota. The prevalence of overweight and obese children is increasing at an alarming rate in the United States and other industrialized countries. Currently, over 22 percent of all children in the United States are overweight. Recent data has shown that obesity is independently associated with coronary atherosclerosis in young adults. The initial development of cardiovascular disease likely occurs during childhood, and obesity may accelerate this process. Furthermore, adiposity in childhood predicts obesity in young adulthood and may increase the risk for future cardiovascular mortality. A recent study has demonstrated that obese, but otherwise healthy children, exhibit vascular endothelial dysfunction and increased arterial stiffness compared to their normal weight peers. These findings are important since endothelial dysfunction occurs very early in the pathogenesis of cardiovascular disease and is considered an initial marker of atherosclerosis. Exercise may be an effective non-pharmacological means by which to improve endothelial dysfunction in overweight and obese children. Studies in adults have consistently shown that exercise training can positively modify endothelial function; however, data are lacking in children. Therefore, the purpose of this study was to examine the effects of exercise training on endothelial function in overweight and obese children and adolescents. Dr. Kaiser has submitted two grants from this activity: Obesity, Exercise, and Vascular Function in Children was submitted to NIH PA-01-017 and Effects of Antioxidant Therapy on Vascular Endothelial Function, Inflammation, and Adhesion in Overweight Children was submitted to the American Heart Association.

Subcutaneous Abdominal Tissue Characteristics in Different Types of Obesity. Yourka Tchoukalova, M.D., Ph.D., Endocrine Research Unit, Mayo Clinic, Rochester, MN. Previous studies have found that preadipocytes from omental fat tissue (considered more insulin resistant) have lower rates of proliferation and differentiation but higher susceptibility to apoptosis than preadipocytes from abdominal subcutaneous (less insulin resistant) fat tissue. Preliminary work shows that the total cellularity of the omental adipose depot is greater than from the abdominal subcutaneous depot but the number of fat cells is similar in both depots. It seems that the fat cell number is fixed and achieved by alteration in the processes controlling preadipocyte or adipocyte cellularity. Synchronous lower rates of preadipocyte proliferation and differentiation but higher susceptibility to apoptosis may be related to insulin resistance. This study proposes that the cellular content and behavioral relationship between subcutaneous abdominal fat tissue in upper body (more insulin resistant) obesity and subcutaneous abdominal fat tissue in lower body obesity (less insulin resistant) is similar to the aforementioned relationship between omental and subcutaneous fat. Conversely, femoral depots (not insulin resistant) from women with upper and

lower body obesity may not have differences in cellularity and processes regulating fat acquisition. Twenty women with upper body obesity and 20 women with lower body obesity will undergo measurements of body composition (DEXA and abdominal CT) and resting energy expenditure and have adipose tissue biopsies (abdominal subcutaneous and femoral subcutaneous). The number of total cells, fat cells, stromal vascular cells, and the percent of preadipocytes from the stromal vascular cells will be measured. Additionally, the rates of proliferation, differentiation, and apoptosis of stromal vascular cultures and cloned preadipocyte cultures will be determined in at least three volunteers with each type of obesity. Dr. Tchoukalova has submitted a grant entitled *In Vivo* vs. *In Vitro* Methods for Assessment of Preadipocyte Dynamics to NIH/NIDDK (NIH/NIDDK1 K01 DK073209-01).

Reduction of Adiposity by Increasing Fructose-2,6-Bisphosphate Concentration in Obese Mice. Chaodong Wu, Ph.D., Department of Biochemistry, Molecular Biology and Biophysics, University of Minnesota. Obesity develops when energy intake exceeds energy expenditure over a considerable period of time. This positive energy balance is due to high energy intake or low energy expenditure, or a combination of these two factors. Regulation of energy balance is essential for the treatment of obesity. Decreasing food intake and/or increasing energy expenditure to regulate energy balance have been shown to reduce obesity. Particularly, acceleration of fatty acid oxidation in the liver is able to reduce obesity, or adiposity, in obese animal models. The enhanced fatty acid oxidation by transgenic modification of genes related to lipid biosynthesis produced an increase in energy expenditure and improved glucose homeostasis. To date, it remains unknown whether direct alteration of glucose and lipid metabolism can regulate energy balance through modulating metabolic pathways instead of by transgenic modification. Fructose-2,6-bisphosphate (F-2,6-P_2) is a regulator that controls glucose metabolism in liver. Increasing hepatic F-2,6-P_2 content via adenovirus-mediated overexpression of 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (6PF-2-K/F-2,6-P_2ase) is able to reduce hepatic glucose output and decrease levels of circulating lipids in obese mice. Indeed, decreases in body weight and adiposity were observed in the obese mice when hepatic F-2,6-P_2 was increased. Also, preliminary studies of mice with high F-2,6-P_2 levels have shown only small decreases in food intake. However, the mechanisms for the reduction of adiposity in the obese mice are not clear. Based on the above observations, we hypothesize that increasing hepatic content of F-2,6-P_2 will decrease adiposity mainly through increasing energy expenditure by accelerating lipid oxidation in the liver. To test this hypothesis, we will study the effects of F-2,6-P_2 on regulation of energy balance by carefully determining food intake and measuring carbon dioxide production and oxygen consumption using indirect calorimetry. By analyzing the ratio of carbon dioxide production to oxygen consumption, the respiratory quotient, the role of high F-2,6-P_2 levels relative to accelerated lipid oxidation in increased energy expenditure will be addressed. This activity led to the successful award of a Minnesota Medical Foundation grant, A Pair-Feeding Study for Regulation of Energy Balance by Enhancing Hepatic Glucose Metabolism in Obese Mice. Dr. Wu has also submitted a grant, Proteomic Study for Coordinated Hepatic Fuel Metabolism, to NIH through an R21.

Non-Exercise Activity Thermogenesis in Prepubescent Children. Lorraine Lanningham-Foster, Ph.D., Endocrine Research Unit, Mayo Clinic, Rochester, MN. Children are becoming less physically active and consuming more calories in their diets. This shift to inactivity and increased food consumption patterns is associated with increased obesity in children. Factors related to obesity in children include the amount of time spent in physical or sedentary activity and the energy expenditure (EE) of activity. In adults, it has been demonstrated that increases in non-exercise activity thermogenesis (NEAT) predict resistance to fat gain in nonobese

individuals. The role of NEAT in pediatric obesity has not been evaluated and may prove to also play a key role in modulating weight gain in children and the genesis of obesity in adults. This study will investigate physical activity in pediatric obesity using unique instruments developed in our laboratory. In examining the components of NEAT in children, our hypothesis in the first specific aim is that the EE associated with walking is the primary predictor of NEAT. Alternatively, we will also measure other components of NEAT (fidgeting) that may contribute more to EE than walking in children as compared to adults. In the second specific aim, we will investigate the effect of body weight change on NEAT in lean prepubescent children. Our hypothesis in the second specific aim is that prepubescent children will have decreased NEAT with an artificially imposed increase in body weight. Together, these studies will provide insight into the role of physical activity in the pathogenesis of pediatric obesity. The data collected in the proposed studies will be used as preliminary data for an initial R01 grant application in the area of pediatric physical activity and obesity. Dr. Lanningham-Foster has submitted a grant to NIH (R21 HDO52001-01) entitled Physical Activity Monitoring in Prepubescent Children.

Novel Approaches to Weight Loss Maintenance. Nancy E. Sherwood, Ph.D., HealthPartners Research Foundation, Minneapolis, MN. Long term weight loss maintenance remains the most critical challenge for obesity treatment. Extending the length of clinic-based treatment has been shown to improve maintenance and key behaviors for successful maintenance have been identified. Treatment studies have incorporated such strategies; however, the most intensive phase of treatment typically occurs during weight loss initiation with the maintenance phase occurring after treatment novelty has faded. Although increasing treatment duration improves weight loss, there is a point of diminishing returns as people eventually stop attending sessions. Recruiting participants who have recently lost weight to a maintenance intervention may be a viable alternative strategy. The optimal mode and timing of maintenance intervention delivery are key issues. One conceptual framework suggests that maintenance will be enhanced by teaching people about key behaviors required for weight loss maintenance and assisting them with the development of these habits. This model suggests that a maintenance program would best be designed similar to a standard weight loss intervention where intervention components addressing maintenance-specific behaviors are delivered to participants on a pre-set schedule. An alternative model recognizes that maintenance is a process that inevitably includes periods of weight regain; the likelihood of maintenance will be increased to the extent that individuals pro-actively respond to setbacks by using strategies to reverse small weight gains. This model suggests that interventions should be delivered in response to participants' progress in weight management, providing personalized assistance when it is most needed. The goal of this study will be to develop and pilot-test two interventions designed to promote weight loss maintenance among participants in a managed care (MCO) setting who have recently lost weight. Study subjects will include HealthPartners (HP) members who are age 19 and older who have lost >5 percent of their body weight during the previous calendar year. Primary goals of this pilot study will be to learn about the best strategies for recruiting participants who have recently lost weight. To this end, several strategies will be used including mailings (e.g., articles in HP-wide newsletters and letters) and clinic-based recruitment. Sixty HP members who have recently lost weight and complete baseline measurements will be randomized to either 1) "usual care" (UC); 2) a "scheduled" maintenance intervention (SMI); or 3) a "personalized" maintenance intervention (PMI). Participants will complete a survey and have their body weight measured again at 6-month follow-up. Although the small number of participants in the pilot study and the relatively short length of follow-up will limit our ability to detect statistically significant treatment group differences, trends will be examined by comparing the amount of weight lost at follow-up in each of the two treatment groups to weight lost in the comparison group. Results of

this pilot study will be used as feasibility data supporting a larger NIH grant application proposing the implementation of a full-scale randomized trial evaluating the efficacy of the two weight maintenance interventions in comparison to usual care over 2 years. Dr. Sherwood has submitted a grant entitled Novel Approaches to Weight Loss Maintenance to NIH/NIDDK (R01 DK068291).

Ecological Momentary Assessment of Obesity. Carol B. Peterson, Ph.D., Department of Psychiatry, UMN. Obesity is one of the most significant international health problems. In spite of the importance of eating behaviors in causing and maintaining obesity, eating patterns are not well understood. The role in psychological precipitants of eating behavior is particularly unclear and has critical implications to understanding the etiology, maintenance, and, especially, treatment of obesity. Previous studies that have assessed eating patterns and their precipitants have relied on retrospective recall of past behaviors or diary methods, both of which are strongly influenced by cognitive biases and may have resulted in data of poor quality. This study proposes to investigate psychological precipitants of eating behavior in obesity using a state-of-the-art measurement technique called Ecological Momentary Assessment (EMA). EMA consists of longitudinal daily sampling that allows for the evaluation of psychological variables in "real time," resulting in more accurate observations and minimizing cognitive biases in self-report and recall. Although previous studies have evaluated psychological precipitants of dieting and binge eating behavior, psychological antecedents of more typical eating patterns among the obese have not been assessed using EMA. This investigation will identify specific psychological precipitants associated with food consumption, including mood, the subjective experience of loss of control, and cognitions about the hedonic value of food and the importance of weight loss. Identifying psychological variables that precipitate eating behavior will facilitate more effective weight loss and weight maintenance treatments as well as the development of more accurate etiological models of obesity.

Altered Exercise Vasodilator Signals in Obese Humans. William B. Schrage, Ph.D., Anesthesia Research, Mayo Clinic. The objective of our research proposal is to gain insight into fundamental vascular control mechanisms in obese humans. Very little is known regarding the hemodynamic response to exercise, or the mechanisms controlling blood flow during exercise in obese humans. Obese humans exhibit endothelial dysfunction and reduced exercise capacity. Animal studies suggest obesity is associated with reduced nitric oxide (NO) mediated vasodilation, enhanced prostaglandin (PG) mediated vasoconstriction, and reduced exercise blood flow. In nonobese adults, inhibition of NO or PGs reduces blood flow in the exercising forearm, suggesting both signals contribute to increasing muscle blood flow. The aim of this study is to determine whether alterations in NO and PGs contribute to reduced skeletal muscle blood flow in obese humans and whether obesity alters the structure, function, and protein expression in muscle microcirculation. We hypothesize inhibition of NO or PGs in lean healthy adults will reduce leg muscle blood flow during exercise. In obese humans, we hypothesize muscle blood flow will be lower than lean adults, and that NO inhibition will not reduce blood flow, but PG inhibition will actually increase blood flow. We will also test this hypothesis in vitro with isolated human skeletal muscle resistance arteries obtained from muscle biopsies. We hypothesize that resistance arteries from obese humans will exhibit altered mRNA and protein expression that result in less NO and PG mediated vasodilation and more PG mediated vasoconstriction along with greater oxidative stress. Results from this study will provide fundamental information toward understanding mechanistic control of muscle blood flow in lean and obese humans. Moreover, we will be the first laboratory to obtain molecular and

biochemical insight into how obesity might alter control of blood flow in human muscle microcirculation.

Effects of Breakfast on Hunger, Mood, and Cognition in Youth (a pilot study). Mark A. Pereira, Ph.D., Division of Epidemiology, UMN. The purpose of the proposed study is to evaluate the effects of eating breakfast and to examine the content of breakfast meals on appetite, mood, and cognitive performance in boys. Eating a nutritious breakfast is an important part of a healthy lifestyle, especially in youth. However, many studies have documented high rates of skipping breakfast among youth. While the literature includes many cross-sectional studies demonstrating inverse associations between breakfast frequency and body weight, prospective and experimental studies are lacking. The few studies that have measured effects of breakfast habits on mood or cognitive skills, while provocative, suffer from a variety of limitations. We hypothesize that children will be less hungry, less irritable, more energetic, and demonstrate superior memory and analytical skills following a breakfast meal in comparison to skipping breakfast. Due to effects of dietary composition on blood glucose and satiety, we further hypothesize that children may be less hungry and perform better on these parameters following a balanced breakfast meal containing whole grain cereal, fruit, and milk than after a refined carbohydrate breakfast meal including a pastry and fruit juice. The proposed study will include a cross-over experimental design in 15 overweight adolescent boys in good health and between the ages of 11 and 14 (middle school). The participants will come to the study site on three separate mornings following an overnight fast. The three clinic visits will be separated by a period of at least two days and will occur on weekends, holidays, or during school vacations. In random order, the three different test meals fed during the morning clinic visits will be 1) water, 2) balanced breakfast, and 3) refined carbohydrate breakfast. Over several hours following the meal we will assess perceived hunger, mood, energy levels, memory and analytical skills. The outcomes will be compared over the three conditions using repeated measures regression analysis. The study findings may provide insight into the role of breakfast habits in modulating energy regulation, behavior, and academic performance, and therefore lay important groundwork to be further developed in larger and longer studies.

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.

Longitudinal Follow-up Study of Patients with Eating Disorders. Scott Crow, M.D. Funding: McKnight Foundation, 7/95 – 6/00.

Generic Studies in Bulimia Nervosa. Scott J. Crow, M.D. Funding: Price Foundation, 1/99 – 12/99.

Generic Studies in Anorexia Nervosa. Scott J. Crow, M.D. Funding: Price Foundation, 1/00 – 1/01.

The Treatment of Binge Eating Disorder. Scott J. Crow, M.D. Funding: NIH/NIDDK R01 DK61912. 2/02 – 1/05.

Increasing Lowfat School/Worksite Vending Choices. Simone A. French, Ph.D. Funding: NIH/NHLBI R01 HL56577-03, 4/01/97 – 3/31/00.

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.

Nonexercise Activity Thermogenesis (NEAT) and Obesity in Mice. James A. Levine, M.D., Ph.D. Funding: Mayo CR75 Scholar Award, 1/99 – 12/01.

Nonexercise Activity Thermogenesis (NEAT) in Humans. James A. Levine, M.D., Ph.D. Funding: NIDDK/NIH R01 DK56650-01. 7/01 – 6/06.

Feeding Inhibition: Mapping of Neural Pathways. Catherine M. Kotz, Ph.D. Funding: Department of Veterans Affairs/Merit Review Type II, 4/98 – 3/01.

Lateral Hypothalamic Hypocretin Pathways Modulating Feeding. Catherine M. Kotz, Ph.D. Funding: NIH/NIDDK R01 DK57573, 5/00 – 4/05.

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.

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.

Feeding Effects of the Melanocortin-4 Receptor Ligands: CNS Sites of Action. Silvia Q. Giraudo, Ph.D. Funding: Department of Veterans Affairs/Merit Review Board, 4/99 – 3/03.

Melanocortins, Opioids and Feeding. Silvia Q. Giraudo, Ph.D. Funding: NIH/NIDDK R01 DK/NS59836-01, 7/01 – 6/04.

High Fat Feeding and Intramyocellular Lipid Abnormality. ZengKui Guo, Ph.D. Funding: NIH/NIDDK R01 DK60013, 8/1/01 – 7/31/06.

Muscular Fat and Insulin Resistance in Dietary Obesity. ZengKui Guo, Ph.D. Funding: NIH/NIDDK RO1 DK067419, 12/1/04 – 11/31/09.

Mechanisms of Drug Induced Pulmonary Hypertension. E. Kenneth Weir, M.D. Funding: Department of Veterans Affairs/Merit Review Board, 4/99 – 3/03.

Food-Borne Antibiotic-Resistant and Extraintestinal Pathogenic *Escherichia coli*. James R. Johnson, M.D. Funding: USDA-CSREES/00-35212-9408, 11/00 – 10/03.

Lipid Turnover in a Mouse Model of Familial-Combined Hyperlipidemia. Elizabeth Parks, Ph.D. Funding: American Heart Association, 1/02 – 12/05.

Strength Training for Obesity Prevention. Kathryn H. Schmitz, Ph.D. Funding: NIDDK/NIH DK60743-01, 3/02- – 7/05.

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.

Does strength training alter IGFBP-2? Kathryn H. Schmitz, Ph.D. Funding: University of Minnesota Cancer Center, 1/02 – 12/02.

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.

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, 08/01/04 – 07/31/05.

Grants submitted

Obesity, Exercise and Vascular Function in Children. Daniel R. Kaiser, Ph.D. Funding: NIH PA-01-017, 08/01/04 – 07/31/09.

Effects of Antioxidant Therapy on Vascular Endothelial Function, Inflammation and Adhesion in Overweight Children. Daniel R. Kaiser, Ph.D. Funding: American Heart Association, 2005 – 2007.

***In Vivo* vs. *In Vitro* Methods for Assessment of Preadipocyte Dynamics**. Yourka D. Tchoukalova, M.D., Ph.D. Funding: NIH/NIDDK 1 K01 DK073209-01, 2005 – 2008.

Proteomic Study for Coordinated Hepatic Fuel Metabolism. Chaodong Wu, Ph.D. Funding: NIH R21.

Physical Activity Monitoring in Prepubescent Children. Lorraine Lanningham-Foster, Ph.D. Funding: NIH 1 R21 HDO52001-01.

Novel Approaches to Weight Loss Maintenance. Nancy E. Sherwood, Ph.D. Funding: NIH/NIDDK R01 DK068291, 12/01/05 – 11/30/09.

Scientific Advances/Accomplishments

Basic Mechanisms Core

Two MN ONRC Participating Investigators, Catherine Kotz, Ph.D., UMN and James Levine, M.D., Ph.D., Mayo Clinic, have been awarded a grant through Minnesota Governor Pawlenty's Bioscience initiative entitled "Non-Volitional Activity in Obesity Resistance: Role of the Brain." The collaborative research grant is a part of the University of Minnesota – Mayo Clinic Partnership for Biotechnology and Medical Genomics. This collaboration continues to be supported by the Basic Mechanisms Core through consultation of data management and technical expertise.

The Basic Mechanisms Core provided further support in determining the function of the S14 gene in lipid regulation. The core facilities were used to develop a mouse in which the mouse S14 gene is knocked out. The knockout model shows that this gene plays a significant role in lipogenesis, and the first studies on this mouse model have been published. More recent studies have shown that this gene is necessary for normal mammary gland lipid synthesis, the growth of pups suckling on moms in which this gene is absent show decreased weight gain, and the S14 gene is a member

of a family of proteins found in a wide number of species. The S14 gene is only present in mammals, but the associated gene was found in species as primitive as xenopus. Most importantly, the S14 gene has been shown to regulate lipogenesis by a unique pathway involved in the allosteric regulation of fatty acid synthase. The manuscript describing these aspects of the knockout mouse is in press in Endocrinology. The mouse model will be extremely helpful in understanding intracellular factors that regulate lipid synthesis and the accumulation of fat.

In one project, the Bernlohr laboratory studies Fatty Acid Transport Proteins (FATP). The FATP has been implicated by a combination of classical and molecular genetic studies to facilitate FA uptake in adipose cells and is hypothesized to be bifunctional, catalyzing both FA flip-flop across planar biological membranes and esterification with CoA. To test this hypothesis, FATP1-his and FATP4-flag were purified and enzymatically characterized as long/very long chain acyl CoA synthetases carrying out ATP-dependent FA esterification with broad specificity for a variety of lipids (C12 to C24). FATP4 is 10 to 40-fold more active than FATP1 and is approximately 3-times more abundant in 3T3-L1 cells than is FATP1. In response to insulin (100 nM) FATP1, but not FATP4, translocates from intracellular sites to the plasma membrane similar to that for GLUT4. There are 293 cell lines stably expressing FATP1 on the cell surface stimulate FA uptake and storage as triacylglycerol while cell lines expressing FATP4 in intracellular sites do not. To evaluate the role of FA influx to produce sufficient AMP to regulate the AMP-activated protein kinase, 3T3-L1 adipocytes stably expressing either shRNA directed to either scrambled or FATP1 sequences were developed. FATP1 knockdown adipocytes exhibit markedly reduced FATP1 (~90 percent reduction) protein expression and differentiate normally but have diminished FA uptake, acyl CoA synthetase activity, and triacylglycerol accumulation. FA influx led to the rapid phosphorylation of AMPK in scrambled adipocytes but markedly reduced phosphorylation in FATP1 knock down cells. Consistent with reduced phospho-AMPK, FATP1 cells exhibited reduced phosphorylation of acetyl CoA carboxylase relative to scrambled adipocytes. These results suggest that in fat cells FATP1 facilitates FA influx and that the product of the acyl CoA synthetase reaction, AMP, regulates AMP-activated protein kinase leading to the phosphorylation and regulation of downstream targets. This study is supported by the National Institutes of Health and the Minnesota ONRC. (Core use: Viral, Real-time PCR, Microarray)

In a second major project, the Bernlohr laboratory studies Fatty Acid Binding Proteins (FABPs). FABPs facilitate intracellular lipid trafficking and more specifically, the efflux (but not influx) of FA from fat cells during lipolysis. FABP null and transgenic animal models have been developed and exhibit increased or decreased levels of adiposity, respectively, compared to wild type C57Bl/6J mice. Stable isotope infusions (collaboration with E. Parks and A. Lange) into FABP null mice resulted in similar conclusions: reduced lipolysis from fat cells with no effect on FA influx. Consistent with a role for FABPs in mediating lipolysis, FABPs from fat cells physically associate with the Hormone Sensitive Lipase and mediate the removal of FFA from the surface of the lipid droplet during lipolysis. In contrast, FABP null mice exhibit increased de novo FA biosynthesis. Real time PCR analysis of target genes in adipose tissue indicates that the expression of the adipose triglyceride lipase (ATGL) and HSL are markedly down regulated in the FABP null animals while being increased in the FABP transgenic mice. Concomitant with changes in lipolysis/lipogenesis, the expression of droplet associated proteins perilipin and S3-12 were also altered leading to an overall decrease in lipid flux in the adipose tissue from null mice and increased in the transgenic. (Core use: Viral, real-time PCR)

Excess dietary carbohydrate that is ingested can be converted to triglycerides through the process of de novo lipogenesis, which occurs predominantly in the liver in mammals. In part, this process

is mediated by the transcriptional induction of key rate-limiting enzymes involved in lipogenesis. The transcriptional induction requires both insulin and glucose signaling pathways. We have been exploring the glucose-mediated pathway that is responsible for transcriptional induction. A candidate transcription factor that mediates this action was recently reported to be ChoRE Binding Protein (ChREBP). ChREBP binds to DNA as an obligate heterodimer with the protein Mlx. To evaluate the role of ChREBP and Mlx in glucose regulation, we prepared dominant negative forms of Mlx and introduced these into adenoviral expression constructs. When transduced into primary hepatocytes, dominant negative Mlx was capable of blocking the normal glucose-mediated induction of mRNAs for many lipogenic enzyme genes, including acetyl-CoA carboxylase and fatty acid synthase. No effect on insulin induction was observed. These studies indicate the ChREBP/Mlx is directly involved in glucose regulation and that this pathway works independently from the insulin-mediated induction by SREBP-1c. The Basic Mechanisms core was instrumental in providing instrumentation and support for performing the RT-PCR measurements used in these studies. A portion of these studies was recently published: Ma, L., Tsatsos, N. G. and Towle, H. C., "Direct Role of ChREBP/Mlx in Regulating Hepatic Glucose-responsive Genes," J. Biol. Chem. 280: 12019-12027 (2005). This work is part of an NIH funded project on Nutritional and Hormonal Regulation of Hepatic Genes.

Cathy Kotz, Ph.D., studies central nervous system gene expression changes before, during and after the development of obesity, and how the gene changes relate to feeding and activity measures. The Basic Mechanisms Core has helped Cathy Kotz incorporate rtPCR and microarray technology into her laboratory procedures. Dr. Kotz uses the Affymetrix gene rat brain gene chip (~33,000 genes) available at academic rates through the University of Minnesota. Dr. Kotz uses real-time rtPCR to test direct hypotheses regarding gene changes associated with physical activity and obesity and to follow-up on results from the microarray work. Several sets of primers of interest have been successfully tried. Some of the experimental results have recently been published and others are under review.

Indirect calorimetry chambers were used to test whether *in vivo* flux measurements in the AP2-/- mouse were consistent with substrate oxidation. The AP2-/- mouse is missing one of the fatty acid binding proteins in adipose tissue and fatty acid turnover data from our laboratory showed that in this mouse, fatty acid efflux from adipose was reduced. However, a surprising observation was that the fatty acid concentration in the blood was still high (even though the flow out of adipose into blood was lower than wild type). The only metabolic explanation for this observation is that the animal was not burning fatty acids in muscle. Thus, it was hypothesized that the dietary fat being absorbed was building up in the blood. The muscle was not burning adipose fatty acids well, nor was it burning dietary fatty acids. Calorimetry data was key to verifying the hypothesis that after meals, the AP2 -/- mouse was burning glucose in muscle, even when on a higher fat diet. These data could be construed to mean that loss of AP2 in adipose caused the mouse to be more insulin sensitive. This project was the collaborative effort of several ONRC investigators, bringing together the basic science expertise of the Bernlohr lab, the *in vivo* techniques of the Parks lab, and the biochemical strengths of the Lange lab to demonstrate how the knock out of a gene in adipose can have a global effect *in vivo* resulting in altered muscle and liver metabolism. (RA Baar, CS Dingfelder, LA Smith, DA Bernlohr, C WU, AJ Lange and EJ Parks. Investigation of *in vivo* fatty acid metabolism in AFABP/aP2$^{-/-}$ mice. American Journal Physiology Endocrinology Metabolism 288: E187-E193, 2005.)

Epidemiology and Intervention Core
The most notable accomplishments of the Epidemiology and Intervention Core in the past year have been contributions to the development of four successful proposals for external research funding. Three of the research grants are part of a programmatic research effort to examine the role of environmental influences on food choices, physical activity, and their potential contribution to the national obesity epidemic. ONRC investigators involved in the projects are leading the development of environmental intervention research nationally and internationally. Descriptions of the funded research grants are listed below.

Obesity Prevention in Metro Transit Bus Operators. This project will evaluate environmental intervention strategies at four bus garages to promote healthful eating and physical activity behaviors in metropolitan bus operators. Healthy vending machine choices and fitness equipment will be targeted in the bus garages and for bus drivers en route. Body weight change after two years of intervention will be measured.

Environmental Intervention for Weight Gain Prevention. This project will assess the efficacy of an environmental intervention in preventing weight gain among adults in eight metro-area worksites. The intervention will include increased availability of healthier foods, increased opportunities for physical activity, self-monitoring of weight, and educational materials for preventing weight gain. Body weight, eating behaviors, and physical activity will be measured.

Fast Food Labeling and Pricing Strategies. This project will examine the effects of nutrition labeling and pricing strategies on consumer choice of foods from fast food restaurants. Food choices and energy intake will be examined under different pricing and nutrition information conditions.

Maintenance-Tailored Obesity Treatment. The present study is a 30-month randomized trial designed to evaluate a maintenance-tailored treatment (MTT) for obesity compared to standard behavior therapy (SBT). The MTT treatment differs from SBT because: 1) it deliberately changes treatment approaches over time instead of keeping them fixed and 2) it focuses on adaptation to change as the core treatment objective.

Novel Approaches to Weight Loss Maintenance. This study involves pilot funding provided to conduct a 6 month randomized trial comparing two newly developed alternative weight maintenance programs to usual care with adult members of a managed care organization who have recently lost weight. Data were used to support the submission of an R01 to conduct a larger scale study.

Community Obesity and Diabetes Prevention Web Portal. Consultation for a health behavior incentives/community-based website development study was submitted to the NIH Small Business Incentive Research Program. It addressed reviewer comments for grant resubmission.

Self-Directed Weight Control in Obesity Management. This was a pilot study to evaluate the effectiveness of an experimental self-directed weight control intervention compared to a control condition. The study provided support for staff, participant recruitment, supplies, subject incentives, postage, and data processing. It supported the development of an NIH grant proposal designed to test the feasibility and effectiveness of a self-help weight loss program.

Approaches to Obesity Treatment in a Managed Care Setting (Weigh-To-Be 2). This study supported the development of a competitive continuation application designed to test a continuous-care model of obesity management for individuals at elevated risk of type 2 diabetes in a managed care organization.

Reducing Obesity in the Workplace: A Randomized Trial. This trial supported the development of an NIH grant proposal to evaluate the efficacy of a two-year, multi-component environmental intervention to prevent excess weight gain among bus drivers working in a major metropolitan area.

Standard Worksite Health Program vs. Activated Consumer. This study provided consultation on project implementation and assessment strategies for a CDC Public Health Research: Health Protection Research Initiative grant application.

Examining the Obesity Epidemic through Youth, Family, and Young Adults: Transdisciplinary Research on Energetics and Cancer. This study supported the development of an NCI center grant application to conduct transdisciplinary research, training, and outreach on obesity and cancer in youth, family, and young adults. The proposed Center will address questions about the etiology, prevention, and treatment of obesity in youth and families, and explore biological pathways that may link obesity to cancer. The proposal involves 17 faculty from the School of Public Health and 9 faculty from 7 other departments.

Pricing Strategies for Food in School Cafeterias. This supported the development of an NIH grant application to examine the influence of simultaneous price increases on less healthful foods and price decreases on health foods on sales in a la carte areas in 14 secondary and middles schools over a two year period.

Weight control behaviors: Short-term effects on body weight, eating and physical activity behaviors, and psychological well-being. This was a pilot study to examine the effect of weight and behavioral self-monitoring on behavioral and psychological outcomes. The Core provided support for processing of dietary intake data.

Box Lunch Portion-Size Pilot Study. This was a pilot study to: 1) assess the feasibility and acceptability of a new research paradigm for testing the long-term influence of a dietary exposure in free living persons and 2) to determine the effect of repeated exposure to a large portion meal (lunch) on total energy intake and body weight over a 10-week period. The Core provided support for personnel, participant food, incentives, and collection of 24-hour dietary recalls and other qualitative measures.

Obesity Prevention in Preschool Aged Children. This provided consultation for an R21 application proposing to develop and evaluate a pilot obesity prevention program targeted toward parents of 2- to 5- year-old children who are patients in pediatric clinics.

The University of Minnesota Obesity Prevention Center (UMOPC). Dr. Robert Jeffery, Director of the Epidemiology and Intervention Core, spearheaded an application to the University of Minnesota Academic Health Sciences unit for a University funded center for obesity prevention dedicated to promoting research and education in the field. This Center was approved in the summer of 2004 and is now beginning to develop programs for interdisciplinary collaboration and obesity prevention research with seed funding from the School of Public Health and recurring

funds from University central administration. The goals of this center are quite similar to the goals of MN ONRC, that is, to stimulate interdisciplinary research on the study of obesity prevention across disciplines at the University of Minnesota. The resources available in this Center also provide a golden opportunity for synergism and joint activities to the benefit of both Centers. The University of Minnesota Obesity Consortium was formed to further facilitate multidisciplinary collaboration and foster cooperation in obesity research, education, and outreach efforts. The Consortium links the two obesity centers at the University, the Obesity Prevention Center, and the Minnesota ONRC. The co-chairs are Drs. Allen Levine and Robert Jeffery.

Health System Subcore at HealthPartners Research Foundation. Support has continued for a Health System Subcore from the Epidemiology and Intervention Core at the HealthPartners Research Foundation, a large managed-care organization in Minnesota. This Subcore is intended to stimulate research on obesity-related issues in a real world healthcare delivery system. This collaboration provides access to large populations and support and consultation around technical areas such as healthcare economics, health system database design and management, and survey implementation. Four research grants on obesity, including one designed to test a continuous-care model of obesity management for individuals at elevated risk of type 2 diabetes, have been submitted to NIH through the Foundation in the past year, and other projects are being discussed.

Eating Disorders Subcore

The Eating Disorders Subcore has made important contributions to our understanding of the treatment, course, and outcome of obesity and eating disorders. These advances have occurred in several areas:

- The Subcore works at the forefront of the assessment of disordered eating and has contributed to our understanding of using structured assessments and newer technologies, including ecological momentary assessment.
- Efforts are ongoing to develop better treatments for eating disorders and the Subcore is involved in supporting four such Federally-funded studies plus numerous additional small pilot studies involving treatment development. The four Federally-funded studies include:
    - Stepped Care for Bulimia Nervosa, R01MH59234, PI: Scott Crow, M.D. Ondansetron for Bulimia Nervosa, R01DK52291, PI: Patricia L. Faris, Ph.D.
    - Vagal Nerve Stimulator Treatment for Bulimia Nervosa, R01DK065167, PI: Patricia L. Faris, Ph.D.
    - Group Treatments for Binge Eating Disorder, R01DK61982, PI: Scott Crow, M.D.
- Third, the core provides support for Federally-funded studies of the pathophysiology underlying obesity in eating disorders. For example:
    - Metabolic Function in Binge Eating Disorder, PI: Nancy C. Raymond, M.D.
    - Obesity as a Risk Factor for Psychopathology, PI: Kerri Boutelle, Ph.D.
- The Subcore also supports innovative pathophysiology pilot studies. For example, a study of serotonin depletion in subjects with anorexia nervosa and their siblings by PI: Monica M. Luciana, Ph.D.
- The core provides increasing focus on the cost effectiveness of treatments and the cost burden of disordered eating.

There continues to be a substantial amount of interaction between ONRC researchers in the Eating Disorders Subcore and the Metabolic Studies Core, both in terms of combined support for Dr. Raymond's project as well as consultation by the Subcore to the Metabolic Studies Core regarding the assessment of eating behaviors and other psychopathology in metabolic studies and in the development of treatments for obesity used in metabolic investigations. Also, the Eating

Disorders Subcore is collaborating with Dr. Allen Levine on a study of dietary restraint in the general population. Finally, a number of investigators from the Epidemiology and Intervention Core utilize the Eating Disorders Subcore.

Healthcare Costs. The Eating Disorders Subcore has worked to an increasing degree in the area of healthcare costs. Two of the three treatment trials currently supported by the Subcore include some of the most thorough attempts to date to examine the cost efficacy of various treatments for eating disorders. In addition, the work supported by the Subcore has resulted in a published manuscript examining cost efficacy of anorexia nervosa treatment. The Subcore Director, Dr. Crow, is a member of the Longitudinal Assessment of Bariatric Surgery (LABS) cost effectiveness working group. Finally, the Dr. Crow has received a K02 award from NIMH which focuses in part on healthcare economics studies.

Eating Disorders Journal Club. The Eating Disorders Subcore has played an integral role in the establishment of a highly successful University of Minnesota eating disorders journal club held monthly which brings together a large number of individuals working in the area of eating disorders and disordered eating as it relates to obesity at this institution. This group of 15 to 20 individuals has had only limited interactions previously and already multiple studies are underway based on the journal club meetings. In addition, a number of people who have been interested only in eating disorders are now planning studies in obesity, and vice versa.

Metabolic Studies Core

The Metabolic Studies Core has facilitated a large number of collaborations and accomplishments that would not have been possible otherwise. The body composition (University of Minnesota and Mayo GCRC's) and the mass spectrometry support have been used by a large number of investigators. Some examples of accomplishments are listed below.

The Role of Visceral vs. Subcutaneous Fat in Regional and Systemic FFA Delivery. Dr. Jensen's major contribution in the past year was a publication that defined the role of visceral vs. subcutaneous fat in regional and systemic FFA delivery (Nielsen S, Guo ZK, Johnson CM, Hensrud DD, Jensen, MD. Splanchnic Lipolysis in Human Obesity. *J. Clin. Invest.* 113: 1582 - 1588, 2004). This effort spanned a number of years and collaborations that were facilitated by the MN ONRC. Partially in recognition of this work, Dr. Jensen received the 2005 Robert H. Herman Memorial Award for outstanding research from the American Society for Clinical Nutrition.

Adipose Tissue Development. Dr. Jensen continues to collaborate with Dr. James Kirkland of the Boston Obesity/Nutrition Research Center on adipose tissue development. Dr. Jensen and Dr. Yourka Tchoukalova (a Pilot and Feasibility Award recipient) are conducting a project examining the differential expression of proteins in preadipocytes cloned from visceral vs. subcutaneous abdominal fat using proteomics approaches. They received a supplemental award to DK45343 (Jensen – PI) to study this process prospectively in volunteers gaining weight as part of one of the studies funded by this grant. Two manuscripts describing the study results have been published (Tchoukalova Y, Sarr M, Jensen, MD. Use of aP2 to Determine the Number of Activated Preadipocytes in Human Adipose Tissue. *Am J Physiol Regul Integr Comp Physiol* 287: R1132-R1140, 2004 and Tchkonia1, T, Tchoukalova Y, Giorgadze N, Pirtskhalava T, Karagiannides I, Forse RA, Koo A, Stevenson M, Chinnappan D, Jensen MD, Kirkland JL. Abundance of Two Human Preadipocyte Subtypes with Distinct Capacities for Replication, Adipogenesis, and Apoptosis Varies Among Fat Depots. *AJP: Endo.* 2005; 288(1): p. E267-E277). These investigators are also collaborating with Dr. Kirkland to collect samples from patients undergoing

elective surgery at Mayo to further identify preadipocyte characteristics. Dr. David Bernlohr helped some of these projects by providing the antibody to aP2. Through this contact, Drs. Bernlohr and Jensen developed additional preliminary data that allowed for a successful competing renewal of one of Dr. Jensen's grants (DK45343); Dr. Bernlohr is now a Co-Investigator on this grant. Dr. Jensen helped Dr. Kathryn Schmitz complete her RO1 grant studies on the effects of weight training in obesity prevention in women. Together they co-mentored an undergraduate student at the University of Minnesota, which resulted in a publication (Potretzke AM, Schmitz KH; Jensen, MD. Preventing Overestimation of Pixels in CT Images of Visceral Fat. *Obesity Research*. 12:1698-1701, 2004). This student has been accepted into the University of Minnesota Medical School.

Vascular Function and Body Composition. Michael Joyner, M.D., of the Mayo Clinic Department of Anesthesiology, joined the Minnesota ONRC largely because one of his research fellows received a Pilot and Feasibility award. This award interested Dr. Joyner in the problem of obesity as it relates to vascular function and body composition. He has continued to collaborate with Drs. Jensen (Nielsen S, Halliwill JR, Joyner M, Jensen MD. Vascular Response to Angiotensin II in Upper Body Obesity. *Hypertension*. 44:435-41, 2004), Nair (Toffolo G; Albright R, Joyner M, Dietz N, Cobelli C, Nair KS. Model to Assess Muscle Protein Turnover: Domain of Validity Using Amino acyl-tRNA Vs. Surrogate Measures of Precursor Pool. *Am J Physiol Endocrinol Metab.* 2003 Nov;285(5):E1142-9) and Rizza (Reed AS, Charkoudian N, Vella A, Shah P; Rizza R, Joyner M. Forearm Vascular Control During Acute Hyperglycemia in Healthy Humans. *Am J Physiol Endocrinol Metab.* 2004 Mar;286(3):E472-80; Vella A, Reed AS, Charkoudian N, Shah P, Basu R, Basu A, Joyner M, Rizza R. Glucose-induced Suppression of Endogenous Glucose Production: Dynamic Response to Differing Glucose Profiles. *Am J Physiol Endocrinol Metab.* 2003 Jul;285(1):E25-30; and Charkoudian N, Vella A, Reed AS, Minson CT, Shah P, Rizza R, Joyner M. Cutaneous Vascular Function During Acute Hyperglycemia in Healthy Young Adults. *J Appl Physiol*. 2002 Oct;93(4):1243-50). In addition, together with Drs. Steven Turner (Hypertension-Mayo Clinic), Bruce Johnson, and Michael Jensen, Dr. Joyner has submitted a program project grant application to examine whether individuals with different beta-2 adrenergic receptor polymorphisms have different cardiac, vascular, respiratory, and lipolysis regulation to adrenergic stimulation. This is possible because of an identified cohort of individuals in Rochester, Minnesota with specific polymorphisms.

Human and Animal Physical Activity and Energy Expenditure. Dr. James Levine's research program directly impacts a series of studies on human and animal physical activity and energy expenditure performed by MN ONRC investigators. Dr. Levine's program has developed cutting edge technology to examine the energy expenditure associated with every day activity (Non-Exercise Activity Thermogenesis, NEAT) and in this fashion he directly collaborates with Drs. Jensen (Levine JA, Lanningham-Foster L, McCrady SK, Krizan AC, Olson LR, Kane PH, Jensen MD, Clark M. Inter-individual Variation in Posture Allocation: Possible Role in Human Obesity. *Science.* 28: 584-586, 2005), Somers (studies in progress) and Nair. These technologies are available to other MN ONRC investigators for planned studies and these include investigators such as Dr. Crow and Dr. Raymond at the University of Minnesota. The animal measurements performed by Dr. Levine not only are germane to his ongoing research program but directly support research particularly that of Dr. Catherine Kotz at the VA Medical Center (Novak CM, Jiang X, Wang CF, Teske JA, Kotz C, Levine JA. Caloric Restriction and Physical Activity in Zebrafish (Danio rerio). *Neurosci Lett.* 2005 Jul 8;383(1-2):99-104. and Kiwaki K, Kotz C, Wang CF, Lanningham-Foster L, Levine A. Orexin A (hypocretin 1) Injected Into Hypothalamic Paraventricular Nucleus and Spontaneous Physical Activity in Rats. *Am J Physiol Endocrinol*

Metab. 2004 Apr;286(4):E551-9). Dr. Levine collaborates with Dr. Cheryl Conover to investigate growth factors and murine metabolism and with Dr. Sree Nair to examine the affect of thyroid hormone on mitochondrial function and muscle (Levine JA, Nygren J, Short KR, Nair KS. Effect of Hyperthyroidism on Spontaneous Physical Activity and Energy Expenditure in Rats. *J Appl Physiol.* 2003;94:165-70). Dr. Levine has built collaborations with Dr. K. Sreekumaran Nair, an established investigator in protein metabolism and aging, and a faculty member in the Endocrine Research Unit at Mayo Clinic and is a co-investigator on one of Dr. Nair's R01 grant. Drs. Levine and Kotz are the PI's of a Minnesota Research grant to study biochemical and biological regulators of NEAT (Drs. Charles Billington, Allen Levine, and Michael Jensen are Co-Is on this grant). Drs. Levine and Jensen have helped Dr. Nancy Raymond with her RO1-funded studies of body composition and energy expenditure (doubly labeled water) in women with binge eating disorder. Dr. Levine collaborates with Dr. Lorraine Lanningham-Foster (a Pilot and Feasibility Award recipient) to examine pediatric NEAT.

Obesity-related Research. ZengKui Guo, Ph.D., a Pilot and Feasibility recipient, has an NIH RO1 and an ADA grant to continue obesity-related research. The support that he received through the Minnesota ONRC and the Metabolic Studies Core has been a contributing factor in furthering his success in this field.

NEAT Children. Lorraine Lanningham-Foster, Ph.D., a Pilot and Feasibility recipient, received an 11th percentile score on her R21 proposal to study NEAT in children. The results of her P/F project were key in providing the preliminary data she needed for a successful application.

Specific Accomplishments

Women's Health. The following are the accomplishments of the Minnesota ONRC in women's health:

- The Epidemiology and Intervention Core supported the development of a successful grant proposal on post-partum weight loss with military wives.
- The great majority of the work of the Eating Disorders Subcore continues to focus on women's health issues; although with increasing work in the areas of binge eating disorder and non-binge eating obese individuals in the last couple of years, some men continue to be studied.
- 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. The results were reported in the Journal of Clinical Investigation last year (Nielsen S, Guo ZK, Johnson CM, Hensrud DD, Jensen MD. Splanchnic Lipolysis in Human Obesity. *J. Clin. Invest.* 113: 1582 - 1588, 2004).
- Dr. Jensen has also examined the effects of the menstrual cycle on meal fatty acid metabolism (Uranga, A; Levine JA, Jensen MD. Isotope Tracer Measures of Meal Fatty Acid Metabolism: Reproducibility and Effects of the Menstrual Cycle. *American Journal of Physiology, Endocrinology and Metabolism*. 288: E547-E555, 2005).

AIDS. Dr. Jensen is collaborating with Dr. Jeanine Albu on a project to examine the effects of rosiglitazone and growth hormone of lipid metabolism in AIDS patients treated with retroviral therapy.

Health Promotion and/or Disease Prevention. The following are the Minnesota ONRC's accomplishments in health promotion and disease prevention:

- The Epidemiology and Intervention Core provided consultation on three grant applications focusing on community-based obesity prevention and three grant applications aimed at diabetes prevention. In addition, the clinical populations section continued to increase the volume of eating disorders therapy development and provision of therapy for pilot projects within larger, Federally funded projects.
- Dr. Lorraine Lanningham-Foster along with Dr. James Levine developed a collaboration with the Foundation for Health Promotion to develop a county wide intervention to improve nutrition and exercise in children in rural Minnesota.
- Dr. L. Olson along with Dr. JA Levine has developed a program in human subject motivation for clinical research involving Minnesota ONRC investigators (Drs. Jensen, Joyner, Nair, Rizza, and Levine). This is to better understand what motivates volunteers and ultimately to increase the public trust in clinical research.
- Dr. Levine served on the Rochester School Board, Olmstead County, Minnesota, and on the Sate Advisory Committee to promote physical activity in children.

Reduction in Healthcare Costs. The Eating Disorders Subcore has worked to an increasing degree in the area of healthcare costs. Two of the four treatment trials currently supported by the core include some of the most thorough attempts to date to examine the cost efficacy of various treatments for eating disorders. In addition, the work supported by the core has resulted in a published manuscript examining cost efficacy of anorexia nervosa treatment. The Subcore Director, Dr. Crow, is a member of the Longitudinal Assessment of Bariatric Surgery (LABS) cost effectiveness working group. The Subcore has provided cost effectiveness analysis consultation for a grant submitted by an ONRC Investigator (Kerri Boutelle, Ph.D.). Finally, Dr. Crow has received a K02 award from NIMH focusing in part on healthcare economics studies.

Professional/Public Nutrition Education Efforts. The following are the Minnesota ONRC's accomplishments in professional/public nutrition education efforts:

- The Eating Disorders Subcore remains quite active in the area of professional and public education with members of the core speaking frequently at local community agencies of various sorts. Dr. Carol Peterson presented on assessment and diagnosis of eating disorders as well as treatment of body images disturbance in workshops at the International Conference on Eating Disorders in April 2005. Dr. Crow presented on the landmark Minnesota Semistarvation Study in November 2004.
- The Epidemiology and Intervention Core continued to sponsor the longstanding and successful assessment training seminar through the Eating Disorders Subcore 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.
- A new seminar series, titled "Health Behaviors: Molecules to Policy", is being sponsored by the ONRC, the OPC, and the Cancer Center. The goal of the series is to discuss research issues that cross-cut energy balance related health behaviors, primarily smoking, eating, alcohol and physical activity.

Benefits and Interactions Resulting from the Existence of the ONRC

Basic Science/Clinical Investigation Interactions. There continues to be a substantial amount of interaction between the Eating Disorders Subcore and Metabolic Studies Core, both in terms of combined support for Dr. Raymond's project as well as consultation by the Subcore to Metabolic Studies Core investigators regarding the assessment of eating behaviors and other

psychopathology in metabolic studies and in the development of treatments for obesity used in metabolic investigations.

Dr. David Bernlohr (University of Minnesota), an expert in the biology of cellular fatty acid trafficking, provided invaluable support and insight for Dr. Jensen for the renewal of an NIH RO1 on the topic of regional fatty acid metabolism. This was made possible because Dr. Bernlohr had visited Mayo to learn which animal body composition techniques would be most useful in helping him understand the implications of his transgenic and knockout mouse models. In the course of the conversation it became apparent that the techniques and skills his laboratory possessed would greatly facilitate studies planned by Dr. Jensen.

Drs. Jensen's and Levine's access to metabolic assessment of whole animals has prompted collaboration with Dr. Cheryl Conover (Mayo Clinic) to characterize her PAP-A knockout mice. PAP-A is a protease that degrades IGFBP-4, one of the IGF binding proteins that sequesters IGF. The presence of PAP-A enhances IGF-1 action. Her knockout mice appear to be resistant to obesity induced by a high fat diet. Dr. Jensen is helping to assess the adipose characteristics of these mice and Dr. Levine is helping to measure the energy expenditure and food intake in these animals.

The Eating Disorders Subcore is collaborating with Dr. JA Levine through the Metabolic Studies Core in the development of a project looking at animal models of antipsychotic-related weight gain.

Bringing New Investigators to Obesity/Nutrition Research. The Epidemiology and Intervention Core has been instrumental in developing new researchers in the obesity field. In particular, Dr. Jennifer Linde has been involved in data analysis and manuscript preparation on several obesity related projects as a Research Associate in the Division of Epidemiology and Community Health. Dr. Linde has implemented a pilot project to test the feasibility and effectiveness of a self-help weight loss program and recently assumed the role of Project Director for an environmental intervention for obesity prevention.

The Eating Disorders Subcore continues to provide consultation and support for Dr. Dwenda Gjerdingen for her proposal regarding postpartum depression and weight change which was funded this year. The Subcore has also played an integral role in the establishment of a University of Minnesota eating disorders journal club held monthly for the last 30 months which brings together the large group of individuals working in the area of eating disorders and disordered eating as it relates to obesity at this institution. This group of 15 to 20 individuals has had only limited interactions previously and already multiple studies are underway based on these interactions. In addition, a number of people who have been interested only in eating disorders are now planning studies in obesity and vice versa.

Dr. Michael Camilleri has received an NIH grant in collaboration with Dr. Jensen to study the effects of polymorphisms in candidate genes on gastric function in obesity. The title of the grant application is "Pharmacogenomics of gastric function in weight and obesity." The support of the Minnesota ONRC Metabolic Studies Core stimulated Dr. Camilleri to use body composition for his studies, which prompted the collaborative effort.

Drs. Cynthia Leibson and Slavica Katusic are newly involved in studies of obesity thanks to a pilot feasibility grant and follow-up contacts from Drs. Su and Jensen.

Dr. John Miles rejoined the Mayo Clinic staff and has become a member of the Minnesota ONRC. He takes advantage of the Body Composition Core and the Biomedical Mass Spectrometry Core for support of his RO1 NIH funded studies of meal fatty acid metabolism.

Thanks to the interactions stimulated by the Minnesota ONRC interactions, Drs. Michael Jensen and Virend Somers are conducting studies as part of an NIH grant (Virend Somers – PI, Michael D. Jensen – Co-PI) entitled "Fat gain and cardiovascular disease mechanisms." This was funded as of 2003 by NHLBI (Grant #HL73211). The Minnesota ONRC provides additional support for the GCRC metabolic kitchen to allow the extra feeding studies to be done and through the body composition core with support for CT and dual energy x-ray absorptiometry.

Leveraging of Other Resources. The Basic Mechanisms Core has collaborated with the University of Minnesota Mouse Microarray Group in the development and use of microarray technology. This has enabled the core to leverage the resources of the University of Minnesota and other investigators outside of the area of obesity to make available technology for the users of the Minnesota ONRC. The core has produced multiple microarray slides based on two different mouse cDNA libraries, one obtained from the NIH (NIA 15K cDNA clone set) containing 15,000 unique sequences and derived from mouse embryos, the other obtained from the NIH supported Brain Molecular Anatomy Project from the University of Iowa containing approximately 10,000 unique cDNA sequences. These arrays have been made available to several members of the Minnesota ONRC and initial studies have been undertaken to identify new responsive genes in multiple different conditions.

The Basic Mechanisms Core has leveraged other grant resources to purchase the respiratory gas exchange equipment. This equipment is used by several investigators within the Minnesota ONRC as well as new investigators entering the field of obesity and nutritional research.

The Basic Mechanisms Core has supported the use of the University of Minnesota Proteomics facility in the early development of studies of abnormal serum proteins in children with the metabolic syndrome. Without Minnesota ONRC support these studies would not have been started.

The Knoll Center of Obesity Research and Education continues to be funded for educational efforts directed at primary care physicians in the Mayo/Minneapolis VA Medical Center area to be accomplished by members of the Minnesota ONRC. The presence of an Obesity/Nutrition Research Center was an important factor in securing these funds for educational activities.

The Minnesota ONRC received a Dean's Commitment from Charles F. Moldow, M.D., Associate Dean for Research Programs in the Medical School at the University of Minnesota. This money is being used to support a part-time secretary, to purchase a computer and office supplies, and to support seminars and faculty meetings.

Support has continued for the Health System Subcore at HealthPartners Research Foundation, which is intended to stimulate research on obesity-related issues in a real world healthcare delivery system. This collaboration provides access to large populations and support and consultation around technical areas such as healthcare economics, health system database design and management, and survey implementation. Four research grants on obesity have been submitted to NIH through the Foundation in the past year and others are being discussed.

Robert Jeffery, Ph.D., the Director of the Epidemiology and Intervention Core, spearheaded an application to the University of Minnesota Academic Health Sciences unit for a University-funded center for obesity prevention dedicated to promoting research and education in the field. It is anticipated that significant collaboration will take place between the MN ONRC and OPC that will facilitate the research and education goals of the centers. The MN ONRC and OPC will almost certainly sponsor joint scientific conferences and dissemination events. Educational seminars and courses already share faculty from these different groups and will continue to do so. Both Centers also sponsor developmental project programs for career development. It is anticipated that it may be possible to share expenses associated with solicitation and evaluation of applications across the groups. The presence of both Centers has already stimulated significant interest among young investigators in training in the obesity area. In the most recent pilot and feasibility project solicitations from the MN ONRC, for example, 31 applications were received for only 3 fundable slots. Since many more than 3 merited funding, the expanded availability of resources from the OPC should be a tremendous boon to the training opportunities available to young investigators at the University of Minnesota.

The Eating Disorders Subcore played a role in the recent funding of a National Center of Excellence in Women's Health at the University of Minnesota. The Center is directed by Dr. Nancy Raymond, a Participating Investigator with the ONRC. The joint effort for the annual Center-wide retreat in spring 2005 resulted in the largest turnout to date.

The State of Minnesota has provided an award to encourage collaboration between the obesity researchers at the University of Minnesota, VA Medical Center, and Mayo. This is undoubtedly because of pre-existing collaborations associated with the Minnesota ONRC.

The Basic Mechanisms Core provided consultation to Dr. Charles Billington in his successful efforts to obtain funding from the Minnesota Medical Foundation to purchase an indirect calorimeter for rodents. These funds supplemented funds from collaborators Drs. Cathy Kotz and ChuanFeng Wang. Dr. Kotz received funds from the VA Research Service and Dr. Wang provided funds from part of his VA Merit Award to purchase the indirect calorimeter.

Educational Activities/Accomplishments

Enrichment Program. The Minnesota ONRC Enrichment Program has two goals: (1) to inform the community within the involved institutions of the progress and accomplishments of obesity research and (2) to incorporate research findings into recommendations and services for educating the general 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 as follows.

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. A new seminar series, titled "Health Behaviors: Molecules to Policy," is being sponsored by the Obesity Prevention Center, the Cancer Center, and Minnesota ONRC. The goal of the series is to discuss research issues that cross-cut energy balance related health behaviors, primarily smoking, eating, alcohol, and physical activity. This

year, Sanofi-Synthelabo, Inc. has provided an unrestricted educational grant through NAASO for an NIH ONRC Educational Seminar Series, a bimonthly educational seminar series on a variety of topics ranging from basic science to clinical obesity.

The MN ONRC has provided speakers across the University and co-sponsored a variety of programs. The Center has placed particular attention on making these obesity talks attractive and relevant to the general educated 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 ONRC has presented at these seminars. The External Scientific Advisory group has participated in our obesity seminar series. The Minnesota ONRC serves the academic community by keeping them 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 geographically dispersed. However, technology has progressed to the point where there is a solution at hand. Live (i.e. real time) web casts of the seminars are now available. The web casts appear on a computer screen with sound showing the PowerPoint presentation, with space to type in questions and comments.

A description of some of the more notable highlights is provided below:

- **The First International Ancel Keys Symposium on Nutrition and Health: The International Obesity Epidemic.** The Division of Epidemiology and School of Public Health designed this Symposium to honor Ancel Keys, M.D., Ph.D., who turned 100 years old in 2004. Dr. Keys had a prolific and influential career, including founding the Laboratory of Physiological Hygiene, one of two groups that combined in 1983 to become the present Division of Epidemiology. His contribution to the School, to the University, and to the wider public health has been unique and of great importance. The topic of this first Symposium was The International Obesity Epidemic. It featured a celebration of Dr. Keys' work, followed by a day of talks on obesity and its causes and prevention by 12 internationally eminent speakers. This event was co-sponsored by the Minnesota Obesity/Nutrition Research Center.
- **Whole Grains & HEALTH: A Global Summit.** The University and Department of Food Science & Nutrition hosted an international Whole Grains & Health Summit on May 18-20. More than 40 internationally renowned researchers presented the latest knowledge on the biological science, behavioral health, and technology of whole grains. Each day included interactive discussions, keynotes, panels, forums for the presentation of papers, poster sessions, and other opportunities to consider the future of whole grains research.
- **Kelly D. Brownell, Ph.D**., Department of Psychology, Yale University, provided the keynote address for the Third Annual School of Public Health Roundtable "Meeting the Challenge of Obesity: Uniting Public Health Research, Practice and Policy." His talk was entitled "Reversing the Obesity epidemic: Courage in the Face of Crisis." Several ONRC investigators participated as speakers, moderators, and breakout session leaders. This event was co-sponsored by the Minnesota Obesity/Nutrition Research Center, along with other sponsors.

- **The Bollum Symposium** in Molecular Biology is hosted annually by the Department of Biochemistry, Molecular Biology, and Biophysics (BMBB) and the Interdisciplinary Program in Signal Transduction and Gene Expression (STAGE). Through the years, the Minnesota ONRC has provided co-sponsorship of several internationally recognized speakers who had a focus on control of genes in metabolism and a particular interest in lipid metabolism.
- **Arline D. Salbe, Ph.D.**, Research Nutritionist, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Clinical Diabetes and Nutrition Section, Phoenix, Arizona, presented two seminars during her visit, one entitled "Determinants of Obesity: Studies in Pima Indian Children and Adults," and the other entitled "Why do people eat what they do? Assessing food intake, eating behavior, and taste preferences as risk factors for obesity." As is typical when the MN ONRC brings in outside speakers, there was opportunity for Dr. Salbe to meet with several ONRC Participating Investigators and their trainees during her visit. The investigators she met with were from several different departments, representing the variety of disciplines spanning the MN ONRC. Dr. Salbe's visit was co-sponsored by the Center for Diabetes Research as part of the City-wide Seminar Series, and by the Department of Food Science and Nutrition.
- **Prevention and Population Treatment of Obesity: A National Summit** has been sponsored by the Mayo Clinic for the past two years to share ideas and solutions, as well as to discuss means of implementing possible approaches to obesity prevention and treatment. This summit occurred in May 2004 and again in June 2005, and the results have been presented in a publication.

Center-wide Retreat. The Minnesota ONRC holds an annual center-wide retreat in the spring. In the past, the program has featured presentations by Pilot/Feasibility Award recipients on the findings of their Center-supported research. In recent years, we have adopted a program featuring round table discussions and have featured guests from outside institutions that have a focus on obesity research. This year's retreat focused on Obesity in Adolescent Girls, with speakers from the Division of Epidemiology at the Mayo Clinic, as well as the UMN Division of Epidemiology. The National Center of Excellence in Women's Health co-sponsored the event and was instrumental in organizing the program and moving to an online system for registration and poster submissions. The poster session, which included presentations invited from the research community at large, was well attended. This forum allows ONRC 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 attendance has increased steadily over the 7 years it has been held.

Ann Forsyth, Ph.D., Design Center for American Urban Landscape, UMN, The Built Environment and Physical Activity

Lisa Harnack, Ph.D., Division of Epidemiology, UMN, Effects of Nutrition Labeling on Fast Food Choices

Simone French, Ph.D., Division of Epidemiology, UMN, Food Pricing, Availability and Promotion: Effects on Student Food Choices in the School Cafeteria

Donald Bishop, Ph.D., Minnesota Department of Health, St. Paul, Minnesota, Walking to School: Obesity Prevention Program in Native American Schoolchildren

Panel Discussion: Guest Speakers and Invited Discussants
Robert Jeffery, Ph.D., Division of Epidemiology, University of Minnesota
Mary Story, Ph.D., Division of Epidemiology, University of Minnesota

Focus Groups. The ONRC has established focus groups based on research interests that provide forums for junior scientists and trainees to participate in discussions with senior scientists to identify overlapping interests and pursue potential collaborative efforts. Focus group meetings have resulted in the generation of 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 ORNC, involving weekly research group meetings at which faculty, fellows, and students interested in obesity and related topics present and discuss their work. One such group is sponsored by the Epidemiology and Intervention Core, while another has been organized among obesity researchers at the Minneapolis VA Medical Center.

Journal Club. A journal club has been organized among researchers and clinicians throughout the Twin Cities focusing on eating disorders and disordered eating as it relates to obesity. This group of 15 to 20 individuals has met monthly for the past 30 months. 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 planning studies in obesity, and vice versa.

Newsletter. The ONRC has published newsletters of the activities, research advances, and accomplishments of the Minnesota ONRC investigators in the past. Recently this information has been disseminated electronically through our 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 ONRC's existence and provide information on the services offered through the ONRC.

Service Brochure. The ONRC has a brochure that summarizes the research services provided by the scientific cores. This brochure is distributed to ONRC participants and other investigators requesting information on the organization and resources of the ONRC. The ONRC has plans to expand upon the brochure to include information about some of the programs sponsored by ONRC, like the pilot and feasibility program and the education enrichment program.

Web-related Activities. The ONRC has constructed its own website, *www.umn.edu/MNOC*, which underwent major reconstruction this past year. The site provides information about the ONRC and summarizes the advances and accomplishments of ONRC participants. An obesity listserv with over 180 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 ONRC-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 University of Minnesota by ONRC Participants. The basics of energy metabolism and balance as well as obesity are taught in the Medical School by Drs. Allen Levine and Charles Billington. Drs. Simone French and Robert Jeffery teach a class on Assessment, Treatment and Complications of Obesity and Eating Disorders in the School of Public Health. Drs. Cathy Kotz and Allen Levine teach a course entitled "The Neural Regulation of Feeding and Energy Metabolism" offered through the Department of Food Science & Nutrition. ONRC Participants provided many lecturers for both courses. A course currently offered on "Obesity and Eating Disorders" is taught

by a team of ONRC Participants covering all aspects of obesity represented by the expertise of the ONRC investigators.

Continuing Medical Education (CME). The Minnesota ONRC collaborates with the Department of Continuing Medical Education at the University of Minnesota is an initiative to heighten awareness of obesity as a major threat to public health. Researchers from the Minnesota ONRC participated in a workshop the CME Department sponsored to educate Minnesota physicians about obesity. Likewise, the Minnesota ONRC has received additional funding from the Department of CME to subsidize the costs of external speakers for the annual Obesity Research Day.

Obesity Research Day. Each year in the fall, the Minnesota ONRC sponsors a one-day program of current findings in obesity. The speakers are members of the ONRC External Scientific Advisory Committee and other nationally recognized obesity experts from outside and within Minnesota. In recent years, the event has been extended to a second day to allow time for the External Scientific Advisory Committee to conduct a site visit/review, in conjunction with Obesity Research Day. The event stimulates significant interest and is quite popular. It has helped to increase awareness of the Minnesota ONRC among the general public.

Center for Obesity Research and Education (CORE). The Minnesota ONRC has received continued funding for a CORE through various private sources. CORE is a national consortium of seven academic centers with research, education, and service programs in obesity that was originally funded through an educational grant from Knoll Pharmaceuticals. Two CORE operations are associated with the Minnesota ONRC: one in Minneapolis under the leadership of Dr. Billington and a second in Rochester under Dr. Jensen's leadership. The CORE's mission reflects the educational goals of the Minnesota ONRC, which is to: 1) provide timely, relevant education and training about obesity to primary care physicians and other healthcare professionals; 2) bring expertise to bear as an educational and informational resource in the field of obesity, nationally and in the individual communities served; and 3) raise the public awareness about the problem of obesity and the risk of excess weight including options for prevention and management in fostering health improvement. The primary activity of the CORE centers within the Minnesota ONRC is education. In Minneapolis, CORE support has allowed a series of obesity workshops that provides continuing education about obesity in an interactive small-group setting. The Mayo group associated with CORE educates about obesity in traditional large-format CME settings, which benefits from the drawing power of the Mayo Clinic.

Mayo Clinic Nutrition in Health and Disease. In the fall, the Mayo School of Continuing Medical Education sponsors a course entitled Mayo Clinic Nutrition in Health and Disease that takes place in St. Paul, MN. This course has taken place annually since 2001. In all but 1 year, speakers from the University of Minnesota/Minnesota ONRC have been invited to present. Almost one full day of the 2-day conference is devoted to obesity. The collaboration between Mayo and University of Minnesota investigators facilitated by the ONRC has clearly improved the course. Several ONRC investigators were on the faculty, including Charles J. Billington, M.D.; Scott J. Crow, M.D.; Donald D. Hensrud, M.D.; Michael D. Jensen, M.D.; James A. Levine, M.D.

Prevention and Population Treatment of Obesity: A National Summit. For the past two years, the Mayo Clinic has sponsored "Prevention and Population Treatment of Obesity: A National Summit" to share ideas and solutions, as well as to discuss means of implementing

possible approaches to obesity prevention and treatment. This summit occurred in May 2004 and again in June 2005, and the results have been presented in a publication (Smith AM, Lopez-Jimenez F, McMahon MM, Thomas RJ, Wellik MA, Jensen, MD, Hensrud DD. Action on Obesity: Report of a Mayo Clinic National Summit. *Mayo Clin. Proc.* 80(4):527-532, 2005). A comprehensive web-based nutrition program has been developed by Drs. Lanningham-Foster and Levine. This includes self-test modules and objective validation questionnaires. It is ready for exporting and is currently undergoing intramural testing.

Eating Disorders Subcore. The ONRC's Eating Disorders Subcore has contributed substantially to professional and public nutrition education efforts with members of the Subcore speaking frequently at a variety of national and local community agencies. Dr. Scott J. Crow, Subcore Director, along with the assessment director for the group, Dr. Carol Peterson, gave a talk to the Minnesota Psychological Association membership on obesity, binge eating disorder, and their treatments in 2000. The talk was selected as one of two encore presentations for that year and was given in April 2002. Dr. Crow gave grand rounds lectures on obesity and binge eating disorder for the Student Health Services at the University of Minnesota; on obesity metabolic issues in psychopharmacology at Gunderson Clinic in LaCrosse, Wisconsin in April 2001; and on treatment of bulimia nervosa at the University of Minnesota's Department of Psychiatry in February 2001. Dr. Crow also gave an invited presentation at the President's Symposium for the Psychiatric Research Society meeting in January 2002 on the topic of full syndromal versus subthreshold anorexia nervosa, bulimia nervosa, and binge eating disorder. Dr. Peterson presented on assessment and diagnosis of eating disorders as well as treatment of body images disturbance in workshops at the International Conference on Eating Disorders in April 2005. Dr. Crow presented on the landmark Minnesota Semi-starvation Study in November 2004. The Eating Disorders Subcore 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.

Public Service. Nutrition education must also extend to the general public. The Minnesota ONRC 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 new information (with respect to obesity and nutrition) that now bombards the general public. 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 ONRC helped to sponsor the National Conference on Childhood and Adolescent Obesity: Prevention and Intervention, and was one of the sponsors of the Third Annual School of Public Health Roundtable "Meeting the Challenge of Obesity: Uniting Public Health Research, Practice and Policy." In fall 2004, a conference was organized to recognize Ancel Keys' 100th birthday. The Minnesota ONRC was involved at several levels. The planning committee included Russell Luepker (chair), Clifford Steer, Charles Billington, Allen Levine, and David Brown. In summer 2004, the ONRC supported a conference "Shaping the Future: Strategies for Addressing Obesity," organized by the MN Society of Public Health Educators. Nicolaas Pronk, an ONRC Participating Investigator, was the keynote speaker, Allen Levine presented, and the ONRC provided support to bring in an additional speaker. Recently, the ONRC provided critical support for both the conference on Healthy

Foods, Healthy Lives: Setting the Agenda, and the Whole Grains & HEALTH: A Global Summit. By sponsoring these types of conferences, the MN ONRC provides forums for discussions of obesity research findings among local investigators and nationally recognized obesity experts.

The ONRC Administration Office maintains a phone bank that fields phone calls from the general 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. The ONRC maintains a volunteer list of over 500 subjects waiting to participate in ONRC-sponsored research. ONRC investigators frequently provide interviews for local news programs and for public radio, and write articles for health newsletters. Members of the Minnesota ONRC regularly participate in the university health television series, "Health Talk and You," as well as many other radio and television outlets. The existence of the ONRC has certainly enhanced the visibility of obesity with respect to the general public.

Speakers List

2004 Series

Patrick Tso, Ph.D., Department of Pathology and Lab Medicine, University of Cincinnati, presented a seminar entitled "Role of Apolipoprotein AIV in Body Weight Regulation and Food Intake." Dr. Tso met with several ONRC Participating Investigators during this visit. This event was co-sponsored by the Department of Food Science and Nutrition.

Kenny J. Simansky, Ph.D., Drexel University, Philadelphia, PA, presented a seminar entitled "A Role for Serotonergic 5-HT1B Receptors in the Inhibitory Control of Eating: A Possible Target for Novel AntiObesity Agents." Dr. Simansky met with ONRC Participating Investigators and their trainees during his visit. This event was co-sponsored by the Minnesota Craniofacial Research Training (MinnCResT) Program.

Dianne Lattemann, Ph.D., University of Washington, Seattle, WA, presented a seminar entitled "I Don't Want a Piece of Pie: Metabolic Hormones and Food Reward." Dr. Lattemann met with ONRC Participating Investigators and their trainees during her visit. This seminar was co-sponsored by the Minnesota Craniofacial Research Training (MinnCResT) Program.

The Minnesota Society of Public Health Educators (MN SOPHE) 2004 Conference. The conference entitled "Shaping our Future: Strategies for Addressing Obesity" was held at Macalester College. The keynote speaker was Dr. Nico Pronk, Vice President, HealthPartners Center for Health Promotion. His keynote address, "The Obesity Epidemic and the U.S. Health Care System," spoke to the impact of the epidemic against the backdrop of an increasing prevalence of obesity, treatment efficacy, cost of obesity, and the role of the healthcare delivery system. The plenary speaker was Allen S. Levine, Ph.D., Director of the Minnesota ONRC. His address, "Why do we eat: A neural network approach," explored the biological issues related to the obesity epidemic, providing an overview of the complex neural network that regulates eating and reviewed some of the specific neurochemicals that affect eating behavior. This event was co-sponsored by the Minnesota ONRC.

Steven K. Clinton, M.D., Division of Hematology & Oncology, The Ohio State University College of Medicine & Public Health, presented a seminar entitled "Energy balance, obesity, and prostate carcinogenesis." This event was co-sponsored with the Cancer Center and Department of Food Science & Nutrition, UMN.

James Ntambi, Ph.D., of the University of Wisconsin, presented a Chalk Talk/Open Forum entitled, "Why should FScN students care about genomics?" and a seminar entitled, "Current work in genomics and nutrition and the future of the field of nutragenomics and how nutragenomics could be integrated into the nutrition and food science undergraduate and graduate programs." This event was co-sponsored by the Department of Food Science & Nutrition.

Healthy Foods, Healthy Lives: Setting the Agenda. This conference was the kick-off event for the Presidential Initiative "Healthy Foods, Healthy Lives." The Healthy Foods, Healthy Lives conference brought together a broad group of University of Minnesota food and health researchers with key external partners to develop an action plan to advance University research and its applications in the area of food and health. The conference began with a public forum featuring plenary lectures on state-of-the-art research and future directions given by internationally known speakers. The purpose of these lectures was to stimulate discussion and interaction among the participants, which was critical for the agenda-setting working conference that followed. The 50-100 invited participants included University of Minnesota faculty, faculty from other academic institutions, scientists and corporate executives from the food industry, foundation executives, government officials, and leaders of professional organizations related to food, nutrition, and public health. The outcome of this conference will be an action plan for the President's "Healthy Foods, Healthy Lives" Initiative.

2005 Series

J. Lee Beverly, Ph.D., of the Division of Nutritional Sciences at the University of Illinois, Urbana-Champaign, presented a seminar entitled "Influence of Obesity on Glucoregulatory Systems in the Hypothalamus." Dr. Beverly met with several ONRC investigators and their trainees during his visit to the MN Obesity/Nutrition Research Center.

Dale A. Schoeller, Ph.D., of the Department of Nutritional Sciences at the University of Wisconsin, Madison, presented a seminar entitled "Where is the Energy? When Diet and Activity Records Don't Match." Dr. Schoeller met with several investigators from the Department of Food Science & Nutrition and the MN ONRC. This seminar was available to the MN ONRC through a simulcast web cast. This seminar was co-sponsored by the Department of Food Science & Nutrition, UMN, and the MN Obesity/Nutrition Research Center.

Sheila Collins, Ph.D., Senior Investigator, Division of Biological Sciences, Director of the Endocrine Biology Program at CIIT Centers for Health Research, presented a talk entitled, "Obesity in the 21st century: Genetics, environmental factors, or both?" as part of the spring Northland Chapter of the Society of Toxicology meeting. The meeting was co-sponsored by the Department of Biochemistry, Molecular Biology & Biophysics, the Division of Environmental Health Sciences, and the Minnesota Obesity/Nutrition Research Center. Dr. Collins presented another seminar entitled, "Mitochondrial Uncoupling Proteins: Regulatory Mechanisms and Role in Metabolic Disease." This presentation was part of the seminar series sponsored by the Department of Biochemistry, Molecular Biology & Biophysics.

Health Behaviors: Molecules to Policy Round Table Series
The overall goal of the seminar series is to discuss research issues that cross-cut energy balance related health behaviors, primarily smoking, eating, alcohol intake, and physical activity. Specific goals of the series: 1) Identify the issues or current research on the topic; 2) Discuss commonalities and how each health behavior area can inform the other; 3) Identify future directions and research areas. Meeting frequency is every two months and it rotates between Medical School, Cancer Center, and School of Public Health. The format is 2-3 individuals providing background information, and roughly 30 minutes of discussion. The first seminar addressed Litigation and Policy Interventions. Sponsored by the Cancer Center, the University of Minnesota Transdisciplinary Tobacco Use Research Center (TTURC), the Minnesota Obesity Prevention Center, and the Minnesota Obesity/Nutrition Research Center.

Robert R. Henry, M.D., Chief, Section of Endocrinology, Metabolism & Diabetes, University of California, San Diego, presented a seminar entitled, "Adiponectine: Metabolic and Vascular Effects," as part of the Endocrinology & Diabetes City-Wide Conference. This conference is sponsored by the University of Minnesota Department of Medicine and the Division of Endocrinology.

Harvey Grill, Ph.D., University of Pennsylvania, presented a seminar entitled "Contributions of Hindbrain and Hypothalamus to the Distributed Neural Control of Energy Homeostasis." Dr. Grill met with several Center investigators and their trainees during his visit. This event was co-sponsored by the Department of Neuroscience and the MN Obesity/Nutrition Research Center.

Yuqing Eugene Chen, M.D., Ph.D., Cardiovascular Research Institute, Morehouse School of Medicine, presented a seminar entitled "Metabolic Syndrome: A Disease for the 21st Century." This seminar was co-sponsored with the Department of Medicine - Division of Endocrinology, the Department of Biochemistry, Molecular Biology and Biophysics, and was part of the City-Wide Seminar Series.

Listing of Core Services

Basic Mechanisms Core

A. DNA Sequencing
This facility has an ABI 310 automated DNA sequencer and a Perkin-Elmer System 2400 thermocycler. We can provide DNA sequence data from plasmids or other vectors as well as PCR fragments. We provide this service at no cost to the user, but ask the user to provide the template and sequencing primer. In addition to DNA sequencing, the ABI 310 is able to perform gene scanning and RFLP type analyses. These services can be made available to investigators associated with the ONRC.

B. DNA Chip Technology
This service is provided in the form of support for the ongoing service within the Health Sciences at the University of Minnesota. The Medical School has acquired several instruments that provide the capability of generating a "chip" containing up to 5000 DNA sequences and analyzing the amount of RNA bound to these sequences simultaneously. Although this does not encompass the total number of genes in the human genome (currently estimated at approximately 30,000 genes), it does represent current state-of-the-art DNA chip technology and permits the investigator to analyze the expression level of a large fraction of the human (or other organism's) genome from

any given tissue. The core currently has available a mouse library containing 10,000 unique sequences that can be used by individual investigators to design their own chip.

C. Quantitative On-line PCR

The Basic Mechanisms Core provides support for real-time quantitative PCR analysis. The Medical School has acquired an ABI 7700 PCR analysis device for its Quantitative PCR Facility, which is available to the members of the Minnesota ONRC.

D. Proteomics Service

The Basic Mechanisms Core provides support for high resolution mass spectrometry of proteins and peptides through the newly developed proteomics laboratory. It is part of the Mass Spectrometry Consortium for the Life Sciences at the University of Minnesota. The Consortium is a core facility with the single purpose of serving the research needs of the life sciences community at the University of Minnesota. The facility provides comprehensive service and expert advice in virtually all areas of mass spectrometry. A Bruker Biflex high resolution MALDI-TOF and a Thermoquest LCQ ion trap electrospray spectrometer are major instruments for protein and nucleic acid work. Both instruments are capable of MS/MS analysis.

The Basic Mechanisms Core is available to provide technical help and service to members of the ONRC. Such help includes preparation of DNA for sequencing, designing primers for sequencing or PCR analysis, and techniques for performing genetic scanning. Additionally, we can provide help in a number of basic molecular techniques including preparation and analysis of mRNA, Southern analysis of DNA, RNA protection assays, DNA cloning strategies, and in situ hybridization. The Core will also develop and provide other services in collaboration with ONRC investigators as needed.

Epidemiology and Intervention Core

A. The Nutrition Assessment Component

The Nutrition Assessment Component of the Epidemiology and Intervention Core incorporates the services of the Nutrition Coordinating Center (NCC) in the School of Public Health. The NCC utilizes a microcomputer-based software system called the Nutrition Data System that maintains a nutrient database that has been referred to as the most reliable and complete nutrient database in the world. The nutrition assessment component provides expertise in dietary assessment methods, including instrument design, data collection, and nutrient analysis.

B. The Data Assessment Component

The data assessment component of the Epidemiology and Intervention Core utilizes the capabilities of the Data Collection and Support Services unit (DCSS) of the Division of Epidemiology, including the Telephone Survey Center. This component provides expertise in population selection, survey design, study participant follow-up, data entry, and database management.

C. The Physical Activity Component

The physical activity component of the Epidemiology and Intervention Core provides access to the Laboratory of Physiological Hygiene and Exercise Sciences under the direction of Dr. Arthur Leon. In this lab, there is an underwater weighing tank for body composition assessment. There is also a treadmill, with capacity for 12 people, and cycle ergometers for determining energy expenditure, for fitness testing or for exercise prescription.

D. The Intervention Component
The intervention component of the Epidemiology and Intervention Core provides investigators with access to the best technologies available for doing nutrition and exercise interventions with outpatient populations, in clinic or community settings. Assistance is available for preparation of grant proposals as well as implementation phases.

E. The Eating Disorders Component
The eating disorders component of the Epidemiology and Intervention Core provides the following services:

- Symptomatic Subject Recruitment
- The Core can provide samples of subjects and, where appropriate, blood and tissue samples obtained from subjects. These sample populations include:
    - Anorexia nervosa subjects
    - Bulimia nervosa subjects
    - Obese subjects with or without binge eating disorder
    - Normal controls obtained to match samples
- Non-Clinical Recruitment
- The Core can provide subject recruitment where appropriate from the general population through advertisements or through the use of other media to publicize individual studies or solicit symptomatic volunteers.
- Standardized Assessment
  The Core provides consultation about, training in, and conduct of detailed and standardized assessment of study subjects using both interview and questionnaire-based methodologies.

F. Statistical analysis consultation is available.

Metabolic Studies Core

A. Body Composition Assessment

- Dual energy x-ray absorptiometry to measure total body fat, fat free mass, and bone mineral density
- Total body water using deuterated water (non-radioactive)—an estimate of fat free mass.
- CT measures of visceral fat
- Extracellular fluid space measurement by radiotracer and biochemical methods
- Circumference measurements for anthropometric characterization

B. Energy Metabolism Measurements

- Total daily energy expenditure (doubly labeled water) - limited amounts of the isotope ($H_2{}^{18}O$) can be provided for highly meritorious studies. Most investigators should seek funding for isotope purchase costs; mass spectrometry analysis available at no charge.
- Resting energy expenditure
- Thermic effect of food
- Exercise thermogenesis

C. Substrate Flux

- Fatty acids, amino acids, glucose - support the design of studies and, whenever possible, the analysis of samples for these studies.

D. Meal Nutrient Partitioning (into muscle and/or adipose tissue)

- Fatty acids, amino acids, glucose – support the design of studies and, whenever possible, the analysis of samples for these studies.

E. Plasma Leptin Concentration Measurements

F. Animal Studies on Energy Balance

- Food intake measurements
- Energy expenditure with activity determinations
- Body composition (*in vivo* using DEXA, or carcass analysis)