University of Pittsburgh Obesity and Nutrition Research Center
Start Date: 1992
Status: Ongoing
Funding Agency: NIDDK
Website: www.pitt.edu/~onrc

Organization and Goals

The University of Pittsburgh Obesity and Nutrition Research Center (ONRC) seeks to facilitate: multidisciplinary research directed toward the prevention and treatment of obesity and research that seeks to advance understanding of the causes of obesity. These goals are of major significance for public health because the majority of adults in this country are overweight or obese, this prevalence is increasing, and childhood obesity has become commonplace.

A major emphasis of the Pittsburgh ONRC is on patient-oriented research. The ONRC supports clinical investigations that range across the entire age span, from prenatal and gestational determinants of obesity and obesity in childhood and adolescence to obesity among middle-aged adults and the elderly. Areas of expertise within our research base include *in vivo* metabolism, body composition, behavioral, pharmacological, and surgical treatments of obesity, and the epidemiology of cardiovascular complications of obesity. There are a number of large clinical trials within our research base, especially in the areas of the relation of obesity to cardiovascular disease (CVD) and diabetes mellitus (DM).

Core Laboratories

The Pittsburgh ONRC is organized into five cores: (1) Administrative; (2) Metabolism; (3) Behavior; (4) Epidemiology; and (5) Laboratory.

Administrative Core.
The Administrative Core promotes awareness of the resources and facilities of the ONRC. It sets criteria for the use of these cores and provides fiscal management of the grant. The Administrative Core prepares reports for the University and NIH/NIDDK, and organizes related activities such as the meeting of the External Advisors. Two other key roles for the Administrative Core are management of the program for Pilot and Feasibility grants and organization of the enrichment program. The Director of the Administrative Core is David E. Kelley, M.D.

Metabolism Core.
The Metabolism Core provides expertise and services for determinations of body composition, energy balance, *in vivo* substrate metabolism and insulin sensitivity, and exercise physiology. The Metabolism Core supports a number of services related to these goals. It is designed to leverage the resources of the ONRC through close interaction with the University of Pittsburgh General Clinical Research Center (GCRC), especially for studies of *in vivo* substrate metabolism. It has similar interaction with the Department of Radiology for bio-imaging of body composition, with the Magnetic Resonance Research Center (MRRC) for MRI and magnetic resonance spectroscopy, and the Positron Emission Tomography Center (PET) for bio-imaging of metabolism. The Director of the Metabolism Core is David E. Kelley, M.D. Bret Goodpaster, Ph.D. is Co-Director for this core.

Behavior Core.
The Pittsburgh ONRC is in its 3rd funding cycle, and since its inception, it has had a strong emphasis on behavioral interventions for prevention and treatment of obesity. The Behavior Core provides facilities, staff, services, and collaborative expertise in studies of eating behavior. In addition to the long-standing focus upon eating behaviors there is a more recently developed sub-core addressing interventions to increase physical activity. The Behavior Core also provides expertise in the analyses of dietary data. The Director of the Behavior Core is Marsha Marcus, Ph.D. Co-Directors are John Jakicic, Ph.D. and Elizabeth Venditti, Ph.D.

Epidemiology Core.
The Epidemiology Core provides expertise in the design and execution of large clinical trials and population-based studies of obesity and nutrition. This epidemiological expertise entails assistance with the collection of clinical outcome data, recruitment of research volunteers, and evaluation of research participants, especially with regard to cardiovascular risk factors. A component of the Epidemiology Core is non-invasive vascular imaging, which helps to enable the study of the relation between obesity and cardiovascular disease in clinical trials. This core is also the fulcrum for the ONRC effort in bariatric surgery. The Director of the Epidemiology Core is Lewis Kuller, M.D., Dr.PH. The Co-Directors are Andrea Kriska, Ph.D., and Kim Sutton-Tyrrell, Ph.D.

Laboratory Core.
The ONRC Laboratory Core consists of three components in support of obesity and nutrition research. Together, they offer expertise and laboratory facilities for biochemical, hormonal, genetic, and stable isotope mass spectroscopy assays. Two of the three laboratory components are the Heinz Nutrition Laboratory and the Human Genetics Laboratory. The ONRC is affiliated with both laboratories, providing partial support to facilitate their efforts in areas relevant to the mission of the ONRC. The third component of the ONRC Laboratory Core is the Mass Spectroscopy Laboratory, formed to provide analyses necessary for the use of stable isotopes to measure substrate flux, substrate oxidation, and energy expenditure. The Director of the Laboratory Core is Rhobert Evans, Ph.D. The Co-Directors are Robert Ferrell, Ph.D. and James DeLany, Ph.D.

The external advisors for the Obesity and Nutrition Research Center are listed in the table below.

Advisor	*Institution*	*Primary Assignment for Review*
Penney Kris-Etherton, PhD	Penn State University	Epidemiology Core
Eric Ravussin, PhD	Pennington Research Center	Metabolism Core
Satish Kalhan, MD	Case Western Reserve University	Laboratory Core
Delia Smith, PhD	University of Arkansas	Behavior Core

Pilot and Feasibility Studies

Current Pilot and Feasibility Studies

The Effect of Vitamin D on Adverse Birth Outcomes in Black and White Women. Lisa Bodnar, Ph.D., M.P.H., R.D., Department of Epidemiology. The objective of this study is to generate pilot data on the vitamin D status of white and black pregnant women in Pittsburgh with normal and complicated pregnancies in order to assess in a future R01 grant the contribution of vitamin D deficiency to racial/ethnic disparities in birth outcomes.

Mechanism of Metformin-mediated Regulation of LKBI-AMPK Association. Martin Schmidt, Ph.D., Department of Molecular Genetics and Biochemistry. The goal of this project is to develop assays for measuring the association of AMPK-LKB1 and ultimately to understand the mechanism by which metformin activates AMPK. The specific aims are to: 1) express epitope-tagged LKB1 in HeLa cells and demonstrate increased association with AMPK in response to metformin treatment by co-immunoprecipitation and 2) apply the bimolecular fluorescence complementation system for assaying AMPK-LKB1 association.

The Effect of BMI and Age on the Yield and Multi-potency of Adipose-derived Stem Cells. Kacey Marra, Ph.D., Department of Surgery. This proposal seeks to further understand the variability in behavior of adipose-derived stem cells (ASCs) from patients with different body mass indices, specifically pre- and post-gastric bypass patients. The goal is to begin to understand the effect of weight loss on the yield of stem cells, the proliferation rate of stem cells, the adipogenic differentiation potential of the cells, and the sensitivity to apoptosis, nuclear architecture, and chromatin mobility.

Metabolic Effects of Large Volume Liposuction. J. Peter Rubin, M.D., Department of Surgery. This study will investigate the metabolic and body composition consequences of large volume liposuction in female volunteer subjects. The investigator's hypothesis is that liposuction will not result in a compensatory size increase of non-treated depots (e.g. visceral abdominal) and that concentration of circulating inflammatory mediators associated with obesity will improve.

Recently Completed Pilot and Feasibility Studies

Regulation of Glucagon-like Peptide 1 Receptor. Allessandro Bisello, Ph.D., Department of Medicine. This project proposed to address the hypothesis that the interaction between GLP-1R and caveolin-1 is a fundamental mechanism by which β cells control both the insulinotropic and the proliferative actions of GLP-1.

Genetics of Obesity and Metabolic Phenotypes in Large Multigenerational African Families. Iva Miljkovic-Gacic, Ph.D., Department of Epidemiology. This study attempted to detect, map, and characterize genes influencing variation in obesity-related traits in a unique collection of Afro-Caribbean families. The investigator tried to determine the extent to which genes (heredity) and environmental covariates contribute to obesity-related phenotypes within extended, multigenerational families of African ancestry.

The Role of Leptin in Hepatic Lipid Partitioning. Wan Huang, Ph.D., Department of Medicine. This study aimed to investigate the acute and chronic effects of leptin on hepatic

triglyceride metabolism in two situations of elevated hepatic lipogenesis: high sucrose feeding and hyperinsulinemia.

Enteral Feeding and Pancreatic Rest. Neeraj Kaushik, M.D., Department of Medicine. The hypothesis of this investigation was that outcome in acute pancreatitis would be improved further if enteral feeding could be given without pancreatic stimulation. Comparisons were made between enteral feeding infused at the level of the duodenum, mid jejunum, and distal jejunum, to assess pancreatic response and amino acid utilization for enzyme and mucosal protein synthesis in healthy human volunteers.

Effects of Social Comparison Feedback and Self-affirmation on Dietary Change. William Klein, Ph.D., Department of Psychology. The goal of this study was to combine social comparison information and self-affirmation into a tailored feedback intervention with the goal of increasing risk perceptions and changes in diet.

Alterations in Hepatic Lipid Metabolism Mediated by Rapamycin: **A New Role for the mTOR Pathway in Regulation of Lipid Metabolism.** German Perdomo-Hernandez, Ph.D., Department of Medicine. The goal of this study was to determine the mechanism(s) by which rapamycin increases mitochondrial FA oxidation and decreases FA esterification/*de novo* FA synthesis in hepatocytes. The investigator attempted to establish the mechanism of these effects by determining how the drug influences flux through specific lipid metabolic pathways and the activity of critical enzymes that regulate those pathways.

Insulin Secretion and Insulin Action in Youth With Type 2 Diabetes Mellitus. Neslihan Gungor, M.D., Department of Endocrinology, Children's Hospital of Pittsburgh. This study aimed to assess the relative roles of insulin deficiency and insulin resistance in the pathogensis of type 2 diabetes of youth and the role that race might play. The investigator compared differences in insulin sensitivity and secretion between African American and American white youth with type 2 diabetes mellitus, and longitudinally evaluated the changes in insulin sensitivity and secretion at diagnosis and after 6 months.

Funding Derived from Previous Pilot and Feasibility Studies

Nutritional Evaluation of Methadone-exposed Mother-Infant Dyads. Debra Bogen, M.D., FAAP. Gerber Foundation.

The Relationship Between Breast-feeding Duration on Obesity in Low-income Preschool Children. Debra Bogen, M.D., FAAP. Funding: BIRCWH Award (local funding).

Insulin Secretion and Insulin Action in Youth With Type 2 Diabetes Mellitus (T2DM). Neslihan Gungor, M.D. Funding: Thrasher Research Fund.

Impact of a PDA-based Dietary Adherence, Intervention on Interdialytic Weight Gain and Blood Pressure. Mary Ann Sevick, ScD, RN. Paul Teschan Award 2/06 – 1/09.

Acceptance of Colorectal Cancer Risk Factor Feedback. William Klein, Ph.D. Funding: 1R03CA101529-01A2 NIH/NCI 4/05 – 3/07.

Muscle Lipid and Insulin Resistance in Aging. Bret Goodpaster, Ph.D. Funding: R01 AG20128-01 NIH/NIA 07/04 -06/08.

Hepatic Fatty Acid Metabolism and Insulin Resistance. Nick Brown, Ph.D. (Primary Mentor), Maja Stefanov-Racic, M.D. (PI). Funding: K08 Mentored Clinical Scientist Development Award NIH/NIDDK 4/01/04 – 3/31/09.

Skeletal Muscle Lipid and Insulin Resistance: Effects of Physical Activity and Weight Loss. Bret Goodpaster, Ph.D. Funding: Clinical Research Award, The American Diabetes Association 1/15/04 – 1/14/07.

Ciliary Neutrophic Factor (CNTF) Receptor Alpha (CNTFRa) Phenotype and Its Relation to Obesity. Stephen Roth, Ph.D. Funding: NIH-NIA R01 3/03 – 2/06.

Ciliary Neutrophic Factor Receptor Alpha (CNTFRa) Genotype and Its Relation to Obesity. Stephen Roth, Ph.D. Funding: R21-NS046021 3/03 – 2/05.

Carnitine Palmitoyltransferase, Fatty acids, and Diabetes. Nick Brown, Ph.D. Funding: American Diabetes Association, Junior Faculty Award 1/01/03 – 12/31/05.

Can the Dexfenfluramine Challenge Test Predict the Weight-loss Response to Dexfenfluramine? Katherine Williams, M.D., M.P.H. Funding: K23-DK02647 1999–2004; R03-DK064171 2003 – 2005.

Psychological Insights and Outcome Following Gastric Bypass Surgery. Melissa Kalarchian, Ph.D. Funding: NIDDK K23-DK62291 8/1/02 – 7/31/07.

Personal and Familial Risk for Eating Pathology in Ballet Dancers. Kelly Klump, Ph.D. Funding: NIMH R03 4/02–3/04; R03-MH065447 5/02 – 4/04.

Behavioral Strategies for Reducing Calorie and Fat Intake: Comparison of Three Approaches. Lora Burke, Ph.D., M.P.H, R.N. Funding: R01-DK58631 5/01 – 4/06.

The Relationship Among Weight Change, Sex Hormones, and Bone Mineral Density in Older Men. Nancy Glynn, Ph.D. Funding: R01-HL66070 2001 – 2006.

Physical Appearance and Health-related Motivations for Weight Loss: Can Enhancement of Motivations Improve Treatment Outcome? Cheryl Smith, Ph.D. Funding: RO1-DK53924, project period not available; RO1- DK58387 9/00 – 8/05.

Gender Differences in Stress-induced Eating. Catherine Greeno, Ph.D. Funding: K01-MH001898 6/1/00 – 5/31/05.

Mechanisms of Hyperleptinemia-induced Improvements in Skeletal Muscle Insulin Resistance in Diet-induced Obesity. Robert O'Doherty, Ph.D. Funding: RO1-DK58855 2000 – 2005.

Behavioral Weight Control for Obese African American Adolescent Women. Linda Ewing, Ph.D., R.N. Funding: R01-HD38425 2000 – 2004.

Developing a Genetic Model With Peripheral Leptin Resistance. Allan Zhao, Ph.D. Funding: American Diabetes Association 2000 – 2004.

Prevention of Weight Gain in Young Women. Mary Lou Klemm, Ph.D. Funding: RO1-DK53942 3/99 – 2/09.

The Effect of Intrauterine Growth Retardation Upon Insulin Resistance and Mitochondrial Function and Gene Expression in the Rat. Robert Lane, M.D. Funding: K08-BD01225 1/99–12/03; K08-BD01225 1/99 – 12/03; American Diabetes Association Research Award 1/99 – 12/01.

Obesity, Liver, and Cardiovascular risk. Monica Yamamoto, Dr.PH., R.D., FADA. Funding: U01-DK57002 1999 – 2004.

The Influence of Obesity on Endogenous Substrate Utilization During Exercise. Bret Goodpaster, Ph.D. Funding: K01-AG00851 9/98 – 8/03.

Visceral Adipose Tissue in Polyp Prevention Trial. Robert E. Schoen, M.D. Funding: K07-CA72561 12/97 – 11/02.

Physician-based Intervention for Obesity and Exercise Promotion. Laurie Simkin-Silverman, Ph.D. Funding: RO1-DK52050 9/97 – 9/02.

Effects of Cereal Feeding on Body Composition and Cholesterol Metabolism in Infants. Carol H. Gilmour, M.D., M.P.H. Funding: NIH-HD30367 12/1/96 – 11/30/99.

Perinatal Imprinting Effect on Hypothalamic Mechanisms Influencing Obesity. Sherin U. Devaskar, M.D. Funding: HD25024 7/1/96 – 6/30/01.

Plasma Acylation Stimulating Protein (ASP): Effects of Weight Loss and Exercise. John M. Jakicic, Ph.D. Funding: HL56127 5/96 – 4/00.

Effect of Obesity on Glucose Transport and Phosphorylation by Skeletal Muscle as Measured by Positron Emission Tomography. Mark A. Mintun, M.D. Funding: American Diabetes Association Feasibility and Development Grant 1/96 – 12/97.

Dietary Modulation of Tumor Suppressor Gene Activity. Richard A. Steinman, Ph.D. Funding: American Institute for Cancer Research 7/95 – 6/97.

Effects of Obesity in Muscle Free Fatty Acid Metabolism. David E. Kelley, M.D. Funding: DK49200 1/1/95 – 12/31/97.

Changes in Substance Use Following Weight Loss/Food Restriction. Kenneth A. Perkins, Ph.D. Funding: NIH-DA04174 9/94 – 8/98.

Ontogeny of Obesity Protein Receptors (OB-R) in Fetal and Neonatal Rats and its Modulation by Prenatal Administration of Steroids. Saroj Parida, M.D. Funding: Local funding agency.

Interactions of the ONRC Within the University of Pittsburgh

There is a strong and diverse research base for obesity and nutrition-related research at the University of Pittsburgh. The primary goal of the Pittsburgh ONRC is to support this research base, in part by serving as a nexus for fostering interaction among researchers. The

ONRC fosters interaction within the research base through several mechanisms. The Administrative Core promotes interaction by raising awareness of ONRC facilities and core services. This is done through the ONRC website and via a quarterly newsletter. Each edition of the ONRC newsletter features one of the four scientific cores, stresses recent activities of the core, recaps information on core services, and provides contact information. The four scientific cores of the ONRC are designed to match the research base and facilitate interaction. Various types of the interactions for each core will be briefly described.

A strong segment within our research base involves epidemiology projects concerning obesity and nutrition. Many of the faculty is based in the Graduate School of Public Health (GSPH). The ONRC Epidemiology Core is led by senior faculty from the GSPH. Also, the ONRC Epidemiology Core, together with the ONRC Laboratory Core, provides three core services that have proven highly useful to the research base in the GSPH. These services are the Ultrasound Research Laboratory for non-invasive vascular testing, the Human Genetics Laboratory, and the Heinz Nutrition Laboratory, which carries out a broad panel of lipoprotein, hormone, and other analyses.

Another strong component of the obesity and nutrition research base is the behavioral interventions of weight loss and physical activity. The Behavior Core of the ONRC is designed to meet the needs of these investigators and promote interaction within this group. A large number of faculty engaged in this research are based in the Department of Psychiatry. Others are based within the Department of Health and Physical Activity and in the School of Nursing. The leadership of Behavioral Assessment and Treatment Core reflects this and therefore is well situated to facilitate interaction.

The Laboratory Core provides a broad range of services to the ONRC research base. Interactions of the Heinz Nutrition Laboratory and the Human Genetic Laboratory with epidemiology investigators have been described. It should also be emphasized that few behavioral investigators operate a “wet-lab” and therefore also rely heavily on these services. The ONRC Mass Spectroscopy Laboratory primarily provides services to investigators who are also utilizing the services of the Metabolism Core. Additionally, the Laboratory Core of the ONRC interacts with basic science investigators. Expertise in complex lipid analyses meets the needs of animal and cellular research as well as clinical investigation.

The faculty of the Metabolism Core is based in the Department of Medicine and its facilities are located adjacent to the General Clinical Research Center. This provides a nexus for interaction with researchers conducting clinical investigations of metabolism or that contain an aspect of body composition research.

An aspect that is especially valuable is the role that the ONRC serves in promoting interdisciplinary interaction across lines of the various cores. For example, an epidemiology researcher may have a need for body composition expertise (and core services) and will be directed to the Metabolism Core. Behavioral investigators may wish to assess various bio-markers of insulin resistance and would be directed for consultation with the Laboratory Core and/or Metabolism Core. Metabolism researchers may wish to assess effects of an intervention of weight loss and physical activity on fatty acid metabolism and seek interaction with the Behavior Core. Each of these exemplifies the type of interdisciplinary interaction that the ONRC provides. The organization of the ONRC is designed to facilitate access to senior faculty for consultation in study design and selection of core services.

Additional to the type of interactions described above are situations in which the ONRC takes a leadership role in initiating interdisciplinary research. The University of Pittsburgh has a strong tradition of participating in large multi-center NIH clinical trials pertaining to obesity and the co-morbidities of obesity. Some examples are the Diabetes Prevention Program, Look AHEAD, TODAY, and LABS. Each of these multi-center NIH clinical trials entails the organization of an interdisciplinary research team, and in this regard, the Pittsburgh ONRC has had a strong leadership role. One example of this is the NIH multi-center study of the effects of bariatric surgery, LABS (Longitudinal Assessment of Bariatric Surgery).

Over the past few years, there have been approximately 1,200 bariatric surgery procedures performed annually at the University of Pittsburgh Medical Center, but until recently, there was a relatively small research component. As part of the mission of the Pittsburgh ONRC "to facilitate and promote multidisciplinary research that seeks effective interventions for the prevention and treatment of obesity," an effort was organized to help develop this research base. The first step in this effort was that the ONRC provided data management expertise and staff to organize a database of clinical outcomes of bariatric surgery, and a journal club was organized to identify areas of research interest. When an RFA was announced by the NIH-NIDDK for a multi-center clinical trial in bariatric surgery, the ONRC helped to organize a successful application for a clinical site. Collaterally, faculty at the Graduate School of Public Health organized a successful application to be the Data Coordinating Center for LABS.

During the past year, a similar type of effort was undertaken by the ONRC to prepare a grant application from the University of Pittsburgh that was submitted to the Pennsylvania Department of Health for support of obesity research. The topic of this application, which will be scored in spring of 2006, is the evaluation and treatment of severe obesity. The ONRC served a central role in the development of this application.

The final aspect of interaction of the ONRC within the University of Pittsburgh that should be addressed concerns those interactions with other research centers. These interactions can be broadly separated into two categories: the first being formal (and budgetary) interaction and the other category being collaborative but without formal structured relationships.

Regarding the first category, from a strategic perspective of trying to most effectively extend and leverage the resources of the ONRC, the four scientific cores are designed so that they complement, rather than duplicate, other research facilities supported by the University of Pittsburgh, the NIH, or other sources of funding. These interactions will be described briefly for each ONRC core.

The Epidemiology Core has a formal interaction with the Ultrasound Research Laboratory located within the GSPH and a close collaboration with the Department of Cardiology electron beam CT vascular imaging facility. There is also close interaction with the Center for Healthy Aging (CDC supported) and the Center for Minority Health within the GSPH. The Laboratory Core has long followed a pattern of providing ONRC support for the Human Genetics Laboratory and Heinz Nutrition Laboratory as a means to leverage ONRC resources and enhance access for obesity research. The Behavioral Assessment and Treatment Core has interaction with the University of Pittsburgh Mind & Body Center, which is another NIH-supported research center, and with Children's Hospital center for obesity treatment and research. The Metabolism

Core has a very strong interaction with the University of Pittsburgh General Clinical Research Center (GCRC) and with the bio-imaging facilities of the PET Research Center and MR Research Center. There is also close interaction with the Department of Radiology, for collaboration in using CT imaging for regional body composition. The other key interaction for the Metabolism Core is between the ONRC Histology Laboratory (which has a light/fluorescence microscope, cryostat, and histology technician) and the Department of Cell Biology Structural Biology Imaging Center, a far larger facility with confocal, live cell, and electron microscopy.

Significant Accomplishments

Physical Activity and Obesity. One scientific theme that is particularly strong at the Pittsburgh ONRC is research concerning physical activity and obesity. A key metric reflecting this interest is that there are services and expertise concerning different aspects of the relation of physical activity to obesity within each of the four scientific cores.

- There is an Exercise Physiology Laboratory within the Metabolism Core, directed by Dr. Bret Goodpaster, an exercise physiologist with expertise in substrate metabolism and body composition research.
- In the Behavior Core, one of the components is designed to provide expertise and intervention material for physical activity interventions in obese children and adults. This effort is led by Dr. John Jakicic, an exercise physiologist with expertise in behavior modification applied to weight loss and exercise.
- In the Epidemiology Core, there is a component developed during the past several years to provide epidemiology researchers with access to a full range of instruments to assess physical activity in population-based research. This component is headed by Dr. Andrea Kriska, an exercise physiologist with expertise in epidemiology research.
- Within the Laboratory Core, one of the newly established core services is measurement of energy expenditure using the gold standard method—the stable isotope doubly-labeled water. Dr. James DeLany, one of the nationally recognized experts in this methodology, provides this service.

Thus, taken together, evaluating the role of physical activity in obesity, measuring fitness and substrate metabolism during exercise, implementing physical activity interventions, or determining rates of energy expenditure attributable to physical activity, there is a comprehensive set of core services and expertise.

The physical activity research supported by the Metabolism Core has made important advances. One of these has been in delineating the importance of exercise in alleviating metabolic inflexibility of fat oxidation in obesity, which is not achieved by weight loss alone. Integral to this line of investigation have been studies examining mitochondrial dysfunction in the pathogenesis of insulin resistance in obesity and type 2 DM, and the effect of exercise in ameliorating mitochondrial dysfunction. This area of research is centered upon analyses of tissue biopsy samples. The physical activity research supported by the Behavior Core has developed innovative approaches for implementing and sustaining physical activity in obesity intervention.

Bio-imaging. Another scientific theme of the Pittsburgh ONRC has been to facilitate the use of bio-imaging modalities for obesity research. This effort is multi-faceted and involves use of PET, MRI / NMR, CT, and vascular imaging. The ONRC has provided support with technical expertise and dedicated software for body composition analysis of MRI and CT images, a service

that has been used by a number of investigators for studies of adipose tissue distribution and tissue composition (e.g., assessment of hepatic steatosis). The ONRC interacts with the PET Center to promote imaging studies of *in vivo* metabolism in muscle and adipose tissue and in the CNS regarding appetite regulation. A major theme that uses bio-imaging has been the study of vascular stiffness and subclinical vascular disease in obesity.

Obesity and Cardiovascular Disease. Obesity is a major risk factor for CVD. Dr. Kim Sutton-Tyrrell, co-director of the ONRC Epidemiology Core, leads efforts examining the relationship between obesity and changes in body fat with aortic stiffening. In 2,500 older adults (mean age 74 years), visceral fat was found to be associated with greater aortic stiffness. Other studies indicated that weight and other variables associated with hyperglycemia and insulin resistance are associated with increased vascular stiffening even in young adults in their 20s and 30s. The WOMAN Study, funded by NIH and now in its 5th year, is testing the hypothesis that non-pharmacological intervention to reduce central obesity, triglycerides, and LDL particles will blunt CV risk, using endpoints of subclinical atherosclerosis and vascular pathology, including carotid intimal medial wall thickness, coronary calcium, and pulse wave velocity. Weight loss at 30 months is averaging 14 lbs for the intervention group versus approximately 1 lb for the Health Education control group.

There has also been a substantial decrease in C-reactive protein and leptin, and increases in ghrelin and adiponectin, all correlated with weight change. In an international project supported by the ONRC, Dr. Akira Sekikawa, collaborating with investigators in Japan and Hawaii, is examining subclinical atherosclerosis in men in Japan, Hawaii, and Pittsburgh. Risk factor profiles for coronary heart disease (CHD) are very similar across the populations, but CHD in Japan is less than half of that in the United States. This study, which includes measurements of subclinical atheroslerosis by EBT and carotid intima media thickness, is examining lipids by nuclear magnetic resonance (NMR) spectroscopy, omega-3 and -6 fatty acids, homocysteine, intra-abdominal fat, as well as other traditional CHD risk factors.

Nationally, there has been a tremendous increase in the number of bariatric surgeries performed to treat severe obesity. The long-term outcomes are not well characterized. Drs. Kuller and Bennet Omalu of the Allegheny County Coroner's Office have tracked outcomes of 16,683 people who underwent bariatric surgery in Pennsylvania since 1995. There have been 440 deaths, with a 5-year mortality of approximately 4.8 percent (CI 4.0-5.9), which is much higher than found in similarly aged Pennsylvania residents. The major causes of death were CHD.

Specific Accomplishments

Women's Health. Dr. Kathleen Mctigue in collaboration with Dr. Kuller, et al. has completed a longitudinal evaluation of approximately 8 years of follow-up among 91,000 participants in the Observational Study of the Women's Health Initiative (WHI) in order to evaluate morbidity and mortality in relationship especially to class II and III obesity among postmenopausal black and white women. This is one of the largest unselected samples for class III obesity women—3,234 – 2,322 white women (3.2 percent of all white women) and 750 black women (9.6 percent of all black women) had BMI >40. All-cause mortality for white women increased from 68/100000 with BMI 18.5-24.9 to 116/100000 with BMI >40, and for black women, 86/100000 to 110/100000. Much of this risk was attributable to the effect of obesity on risk factors of diabetes and hypertension, as well as effects of cigarette smoking and use of lipid-lowering drugs. Waist circumference but not hip circumference was strongly related to mortality within each BMI

category. These results show that risk factors such as hypertension, diabetes, and elevated lipids account for much of the excess mortality associated with obesity and that waist circumference is a powerful predictor within BMI categories, at least up to class III BMI.

Aging Population. The age-related changes in body composition, loss of muscle function, and metabolic dysregulation have been an active area of investigation at the ONRC. Dr. Goodpaster's clinical investigations are currently examining the effects of exercise and weight loss on body composition, skeletal muscle lipid accumulation, fatty acid metabolism, and insulin resistance in older men and women at risk for the development of type 2 diabetes mellitus. Results of these projects indicate that regional fat distribution is an important component of the metabolic syndrome and type 2 diabetes in older adults. Moreover, these studies demonstrate that older adults are quite responsive to increased physical activity as evidenced by robust improvements in metabolic function, including improved insulin sensitivity and the oxidative capacity of skeletal muscle. Aging and obesity seem to share many similar characteristics, and these ONRC-supported studies continue to provide important new evidence in both aging and obesity related dysfunction.

To assist in a new project involving elderly women and men, the LIFE Study (NIH-NIA U01 AG022376-01), under the direction of Drs. Anne Newman and Bret Goodpaster, created an exercise facility. This is an ONRC facility that provides treadmill and stationary cycles, along with special exercise equipment for these elderly participants. The facility is also used by several other ONRC investigators and is for the sole use of research volunteers who are participating in exercise studies. This facility enables investigators to provide multiple options to participants for their exercise sessions.

AIDS. The ONRC has continued to provide support for AIDS research, primarily in the area of body composition. Dr. Sharon Riddler of the Division of Infectious Disease is examining the effects of anti-HIV therapy upon body composition and uses the ONRC DEXA as part of this project. The Multi-center AIDS Cohort Study is a study which involves groups from Johns Hopkins University, Northwestern University, University of California, Los Angeles, and the University of Pittsburgh. This study analyzed lipids in homosexual and bisexual men infected with the HIV virus before and after seroconversion and after treatment with highly active antiretroviral therapy (HAART). The results indicate that HIV infection causes substantial decreases in serum TC, HDLc, and LDLc levels, whereas subsequent HAART elevates TC.

Health Promotion and/or Disease Prevention. In the Behavior Core, Dr. Jakicic's research has examined the ability of obese participants to adopt and maintain various doses and intensities of physical activity over a 12-month intervention. Dr. Jakicic has also been prominent in demonstrating that 200 to 300 minutes per week of moderate intensity physical activity is an important component of a comprehensive weight-loss program.

The ONRC continues to support Action for Health (LOOK AHEAD), the NIH-NIDDK clinical trial of the long-term effects of moderate weight loss and increased physical activity on cardiovascular health and disease prevention in patients with type 2 DM. Also, the ONRC is involved in the intervention and prevention trials for type 2 DM in adolescence. During the past year, the Director and Associate Director of the ONRC and various core directors have met on a regular basis with the leadership of the Allegheny County Medical Society and the UPMC Health Plan, as these entities seek to develop obesity awareness and treatment plans. These plans entail both professional and lay population awareness and education.

Benefits and Interactions Resulting from the Existence of the ONRC

Two examples of interaction of the ONRC with basic science and the promotion of interaction with clinical investigation will be briefly described. Dr. Allan Zhao of the Department of Cell Biology has found several leptin interacting proteins in serum that appear to confer leptin resistance in obesity. Isolated using leptin-affinity chromatography, mass-spectrometry revealed that one is C-reactive protein (CRP). The project is examining both human samples and basic science animal research components to determine how CRP-leptin interactions inhibit the binding of leptin to its receptors and blocks its ability to signal.

Another interaction has been between clinical investigations by the Kelley laboratory concerning impaired fat oxidation by skeletal muscle in obesity and basic scientists examining regulation of the β-oxidation pathway of fatty acid catabolism. This will examine whether there is a build up of incomplete products and of chain length longer than two carbons as a consequence of a reduced capacity of the electron transport chain to accept electrons generated in the β-oxidation pathway, and will examine blood patterns of acylcarnitines.