

New York Nutrition Obesity Research Center

Start Date: 1979

Status: Ongoing

Source of NIH Support: NIDDK

Website: <http://www.nyorc.org>

Organization and Goals

The goals of the New York Nutrition Obesity Research Center (NY NORC) are to:

- Bring and hold together, under the Center's umbrella, a "critical mass" of investigators of separately funded research projects who share a strong interest in the study of obesity-related problems.
- Use funds allocated for the support of pilot and feasibility projects and for program enrichment to promote and test new research ideas, stimulate productivity, foster the development of new investigators in the field, and persuade scientists in disciplines not ordinarily concerned with obesity (e.g., molecular biology, molecular genetics, biophysics) to become involved in obesity-related research problems.
- Provide participating investigators of funded projects relevant to obesity research with valuable laboratory, technical, and educational services that otherwise would not be available to them, thereby improving the productivity and efficiency of their operations.
- Train basic investigators, clinical investigators, postdoctoral fellows, medical students, and doctoral students in basic medical sciences and postdoctoral fellows in obesity and related eating disorders research.
- Engage in enrichment activities that will inform and stimulate the scientists attached to the NY NORC to greater research productivity in the field of obesity.

The NY NORC is a combined effort of St. Luke's-Roosevelt Hospital Center (SLRHC), Columbia University Medical Center (CUMC), and Albert Einstein College of Medicine (AECOM), with Core Laboratories located in the three institutions, and pilot and feasibility studies being funded there and elsewhere in the New York area.

The NY NORC is made up of 11 Cores, eight of which are funded by the NORC, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) grant; two are funded by the Clinical and Translational Science Award through their inpatient and outpatient clinical research facilities at CUMC and SLRHC, National Institutes of Health (NIH) grant; and one is self-sustaining.

Core Laboratories

Administrative Core at St. Luke's-Roosevelt/Columbia: F. Xavier Pi-Sunyer, M.D., Director;
Rudolph Leibel, M.D., co-Director

External Advisory Group Members:

Claude Bouchard, Ph.D., Pennington Center, Louisiana State University

Timothy Moran, Ph.D., Johns Hopkins University
Joseph Nadeau, Ph.D., Case-Western Reserve University

Biostatistics SubCore (of Administrative Core): John Thornton, Ph.D., Director
Body Composition Core: Dympna Gallagher, Ph.D., Director
Energy Expenditure Core: Jeanine Albu, M.D., Director
Hormone and Metabolite Core: F. Xavier Pi-Sunyer, M.D., Director
Human Ingestive Behavior Core: Harry Kissileff, Ph.D., Director
Molecular Genetics/Molecular Biology Core: Rudolph Leibel, M.D., Director
Adipose Tissue Core: Yiying Zhang, Ph.D., Director
Animal Phenotyping Core: Gary Schwartz, Ph.D., Director

Cores Not Supported Under NIH NORC Grant

- **Columbia Clinical and Translational Science Award (CTSA) Inpatient and Outpatient Core (at Columbia-Presbyterian Hospital):** Henry N. Ginsberg, M.D., and Melissa D. Begg, Ph.D., Directors
- **Columbia CTSA Satellite Inpatient and Outpatient Core at St. Luke's-Roosevelt Hospital:** Jeanine B. Albu, M.D., Director
- **Weight Loss Program of the NY NORC, Ambulatory Program:** F. Xavier Pi-Sunyer, M.D., Medical Director; Richard Weil, M.S., and Betty Kovacs, M.S., Associate Directors

Core Activities

The Core Laboratories have all remained very busy. This is confirmed by the large number of publications emanating from the NY NORC. The Cores have helped individual investigators and groups of collaborating investigators in their pursuits. These Core Laboratories continue to provide support that allows for greater efficiency and productivity by the member faculty of the NY NORC.

The NY NORC has led to multiple research collaborations that resulted in scientific advances in obesity. One focus is on the genetics of obesity, an effort to identify genes that are responsible for animal and human disease. Another is body composition, with efforts to improve the methodology for measuring fat, lean body mass, bone, and skeletal mass, and the use of the technology to document the effect of various diet and exercise interventions on body composition changes. The use of imaging through magnetic resonance continues to be actively pursued. Another area of focus is on energy expenditure, particularly trying to document the expenditure activity of individual organs. There is also a continuing effort to unravel the role of gut peptides in human food intake regulation and to identify some of the genes responsible for this regulation. The natural history and characteristics of bulimia, binge eating, and night eating are also being studied. Ingestive behavior is studied along with functional magnetic resonance imaging (fMRI), to gain insight into the role of various areas of the brain in appetite regulation. A continuing effort is being made to determine the role of various fat depots in insulin resistance, and the differential impact of these depots on differing racial groups. Finally, a number of multi-center clinical trials relating to weight loss and outcomes of disease are under way. Collaborations among investigators are multiple and strong. The use of Core Laboratories for

training, consultation, and service is high. Some of the advances from collaborative studies in the past year are described below.

The high-quality research that the NY NORC fosters is attested to by the high publication rate of the users of the Cores. The users are individuals who have current peer-reviewed funding in the area of obesity and eating disorders. The privileges of membership are use of Core facilities, consultation on design of projects and methodology, training in methodology, and participation in enrichment activities of the Center. Members engage in enrichment by presenting protocols, results of studies, and projected future experiments to the membership. Concrete evidence of the quality of the research being conducted in the NY NORC can be found in four items: the kinds of journals in which the investigators publish, the impact these publications have on continued research, the total number of publications, and the sustained research funding of the NY NORC users.

Pilot and Feasibility Studies

Active Pilot and Feasibility Grants

- **Christopher N. Ochner, Ph.D.**, SLRHC and Columbia University
“Effect of Roux-en-Y Gastric Bypass Surgery on Brain Activation in Fasted and Fed Conditions”
- **Clemence Blouet, Ph.D.**, Albert Einstein College of Medicine
“Role of Mediobasal Hypothalamic *Crtc1* in the Regulation of Energy Balance in the Mouse”
- **Kevin Kalinsky, M.D.**, CUMC, Columbia University
“Pre-Surgical Intervention Study To Evaluate the Effect of Metformin on Breast Cancer Proliferation”
- **Edward Colt, M.D.**, SLRHC and Columbia University
“Comparing the Ability of High Resolution Peripheral Quantitative Computerized Tomography (HR-pQCT) with DXA for Measuring Bone Mineral Density in Obese Patients”

Funding Derived from Previous Pilot and Feasibility Studies

- **Metabolic Response to Weight Loss in Older Obese Women.** Dymrna Gallagher, D.Sc.
Funding: NIH, F32 Award, 1/96; NIH, R29, 12/97–11/02
- **Does Weight Loss Reduce Mortality Rate Among Obese Rats?** Joseph R. Vaselli, Ph.D.
Funding: NIH, RO1 DK54298-01, 1/00–11/03; Knoll WRISC Research Award, 7/99–6/01; Pacific Health Care, Inc., 12/98–1/00; Pfizer Central Research, 12/99–11/01
- **Genetic Linkage Studies of Bitter Taste Perception.** Danille R. Reed, Ph.D.
Funding: NIH, RO1, 12/99–11/02; NIH, DK03509, 12/99–11/01
- **Mapping Genes for Body Weight and Fatness in Mice.** Danielle R. Reed, Ph.D.
Funding: NIH, DK55853, 12/99–11/02
- **Relationship of Adipocyte Size and Leptin Gene Expression in Rat Adipose Tissue.** Yiyang Zhang, Ph.D.
Funding: Diabetes Action Research and Education Foundation, Research Grant, 1/99–12/99; American Diabetes Association Career Development Award, 1/99–12/02

- **Effects of Glucocorticoids on Leptin in Human Obesity.** Blandine Laferrere, M.D.
Funding: American Diabetes Association, 1/98–12/01; NIH, KO8 Award, 5/98–3/03
- **Career Development Award.** Blandine Laferrere, M.D.
Funding: American Diabetes Association, 1/1/98–12/31/01
- **Development of a Genetic Resource: The Molecular Genetics of Obesity in Alaska Natives.** Bert Boyer, Ph.D.
Funding: NIH, F33 Award, Senior National Research Fellowship, 1/99–1/00
- **Molecular Mechanisms of Metabolic Suppression: Protein Synthesis and Mitochondrial Respiration in a Hibernating Ground Squirrel Model.** Bert Boyer, Ph.D.
Funding: Department of Defense EPSCoR, Office of Naval Research Grant, 2001–2004
- **Building a Center of Biomedical Research Excellence for Alaska Native Health Research.** Bert Boyer, Ph.D.
Funding: NIH Centers of Biomedical Research Excellence Grant (Co-PI), 2001–2006
- **Familiarity of Caloric Compensation in Young Children.** Myles Faith, Ph.D.
Funding: NIH, KO8 Award, 9/93–9/98; NIH, RO3 Grant, 3/97–3/99; CDC Research Grant, 9/99–8/00; NIH, RO1 Grant, 7/98–1/03
- **Analysis of the Roles of Preopiomelanocortin (POMC) and Agouti-Related Protein (AGRP) in Obesity.** Judith Korner, M.D., Ph.D.
Funding: NIH, KO8 Award, 5/01–4/06
- **Neural Populations Mediating Leptin Action.** Timothy Kowalski, Ph.D.
Funding: NS award, 1998–1999; American Diabetes Association, 1999–2000; now working in pharmaceutical industry as investigator
- **Molecular Mechanisms of Taste Memory in Mouse Insular Cortex.** Michael W. Swank, Ph.D.
Funding: Baylor College of Medicine Startup Intramural Investigational Funds, 1/00–1/03
- **Sarcopenia: Muscle Loss in Elderly African-Americans.** Dympna Gallagher, Ph.D.
Funding: NIH, R29 Award, AG14715, 9/97–8/02
- **Body Composition: Methods, Model, & Clinical Approach.** Dympna Gallagher, Ph.D.
Funding: NIH, PO1 Award, DK42618, 7/01–6/06
- **MRI Derived Organ and Tissue Mass Changes with Weight Loss.** Dympna Gallagher, Ph.D.
Funding: NIH, RO1 Award, HL70298, 9/01–8/04
- **Clinical Trials Pilot Study.** Judith Korner, Ph.D.
Funding: New York Presbyterian Hospital, 7/01–6/02
- **Characterization of a New Murine Neurological Mutant.** Wendy Chung, M.D., Ph.D.
Funding: Children's Health Research Center, P30 Award, HD34611, 12/97–11/02
- **International Consortium for Identification of Genes for Type II Diabetes and Obesity.** Wendy Chung, M.D., Ph.D.
Funding: Eli Lilly, Co., 3/98–3/03
- **Molecular Mechanisms for Regional Differences in Adipose Tissue Gene Expression: Possible Role for Leptin.** Yiyang Zhang, Ph.D.
Funding: American Diabetes Association, 1/99–12/02
- **Molecular Mechanisms for Leptin Effects on Insulin Sensitivity of Hepatic Gluconeogenesis.** Yiyang Zhang, Ph.D.
Funding: Diabetes Action Research and Education Foundation, Research Award, 1/99–12/99

- **Gene Expression and Insulin Resistance.** Anthony Ferrante, M.D., Ph.D.
Funding: Russell Berrie Foundation's Naomi Berrie Award, 1/00–12/02
- **Gene Expression in Leptin-Regulated Pathways.** Anthony Ferrante, M.D., Ph.D.
Funding: NIDDK, K08 Award, DK59960, 4/02–3/07
- **Does Weight Loss Reduce Mortality in Obese Rats?** Joseph R. Vaselli, Ph.D.
Funding: NIH, RO1 Award, DK54298, 2/00–1/04
- **Evaluation of the Potential Effects of Herbal Extracts on Muscle Growth in Guinea Pigs.** Joseph Vaselli, Ph.D.
Funding: US Drug Enforcement Agency Award, NBCHC010064, 10/01–9/04
- **Life Extension by Caloric Restriction: Role of Leptin.** Simon Klebanov, Ph.D.
Funding: NIH, RO1, 9/01–8/05
- **BRCA Founder Mutations among Jewish Participants of the Long Island Breast Cancer Study Project.** Wendy Chung, M.D., Ph.D.
Funding: Academic Medical Development Corporation, 6/1/03–7/1/05
- **Cloning of a Type 2 Diabetes Modifier in Obese Mice.** Wendy Chung, M.D., Ph.D., and Rudolph Leibel, M.D.
Funding: NIDDK, 9/30/03–9/27/07
- **Does Weight Loss Reduce Mortality in Obese Rats?** Joseph Vaselli, Ph.D.
Funding: NIDDK, DK54298, 2/01/00–1/31/04
- **Evaluation of the Effects of Dietary-Derived Steroids on Muscle Growth in Guinea Pigs.** Joseph Vaselli, Ph.D.
Funding: U.S. Drug Enforcement Agency, 3/1/02–2/28/05
- **Intramuscular Adipose Tissue Assessment by MRI.** Dympna Gallagher, Ph.D.
Funding: NIH Contract, 8/1/01–7/31/03
- **Metabolic Effects of Differential Organ Growth Rates.** Dympna Gallagher, Ph.D.
Funding: NIH, HD042187, 9/1/03–8/31/08
- **PPAR-gamma Agonists, Weight Gain, and Fat Redistribution.** Julia Johnson, Ph.D.
Funding: NIH, K-Award, KO1, DK061629, 12/1/02–11/30/05
- **Identification of Genes Mediating Beta Cell Growth, Proliferation, and Survival in Response to Immune Assault and Metabolic Stress.** Anne-Marie Brillantes, M.D.
Funding: New Jersey Foundation for Diabetes Research, 2002
- **Glucose-Induced Genes Regulating Pancreatic Beta Cell Mass.** Anne-Marie Brillantes, M.D.
Funding: NIDDK, KO8 Award, 2002–2007
- **Mechanism of Positive Energy Balance in PROP Non-Tasters.** Kathleen Keller, Ph.D.
Funding: NIDDK, KO1 Award, DK068008, 8/05/05–6/30/10
- **Neuroendocrine Regulation of Energy Homeostasis with Diet and Surgically Induced Weight Loss.** Judy Korner, M.D., Ph.D.
Funding: NIH, RO3, DK067433, 4/01–3/06
- **Metabolic and Hormonal Effects of Bariatric Surgery.** Judy Korner, M.D., Ph.D.
Funding: NIH, RO1, DK072011, 9/05–8/10
- **Effect of Glycemic Index of a Preload on Food Reinforcement in Humans.** Jennifer Nasser, Ph.D.
Funding: International Life Sciences Institute, 2004–2005

- **Improving the Energy Cost Estimation of Physical Activity.** Kuan Zhang, Ph.D.
Funding: NIH, KO25, DK067976, 7/04–6/09
- **Leptin Production and Action in Adipocytes.** Yiying Zhang, Ph.D.
Funding: NIH, RO1, DK063034, 7/03–6/08
- **Cortisol Stress Response and Intake in Binge Eating Disorder.** Marci Gluck, Ph.D.
Funding: NIH, RO3, DK068392, 2005–2007
- **Evaluation of Changes in Central Dopamine by Electroretinography.** Jennifer Nasser, Ph.D.
Funding: ILSI, 2004–2008; NIH, R21 DK076748, 2008–2010; Wrigley Science Award, 2009–2010
- **The Pattern of Daily Physical Activity for Subjects with Metabolic Syndrome.** Kuan Zhang, Ph.D.
Funding: NIH, KO25, DK067976, 7/04–6/09
- **Analysis of Gene Expression Profile of Preadipocytes.** Yiying Zhang, Ph.D.
Funding: NIH, R01, DK063034, 7/1/03–6/30/09
- **Hypothalamic Feeding Circuits in Mouse Models of Gestational Diabetes.** Lori Zeltser, Ph.D.
Funding: American Diabetes Association Research Award, #7-07-RA-195, 7/1/07–6/30/10
- **CD36: a Putative Taste Receptor for Dietary Fat in Humans.** Kathleen L. Keller, Ph.D., and Wendy Chung, M.D., Ph.D. 07/01/06–06/30/08
- **Dixon Imaging Method in Quantifying Bone Marrow, Liver, and Pancreas Fat.** Wei Shen, M.D.
Funding:
 1. ECRIP Grant: New York Empire State Career Development Award; New York State-Empire Clinical Research Investigator Program, 07/01/08–06/30/10. Central Obesity and Health Risk across the Life Span: Optimal MRI Measurement & Location in Adults and Children
 2. R21DK082937 (W. Shen, PI), 06/02/09–05/30/11. Imaging evidence: Is there competition between marrow fat and bone?
- **Effect of Roux-en-Y Gastric Bypass Surgery on Brain Activation in Fasted and Fed Conditions,** Christopher N. Ochner, PhD, SLRHC, Columbia University
Funding:
 1. TRANSFORM K12 , Ochner (PI); NIH/Columbia University CTSA 7/1/2009 – 6/31/2011. Changes in Brain Activation and Appetite-Related Hormones following Bariatric Surgery for Obesity

Scientific Advances/Accomplishments

The scientific accomplishments of the NY NORC are directly related to the ability of the various Core Centers and Core Center directors to aid individual teams of investigators with regard to their respective support needs. Several areas of accomplishment are summarized below. The advances were published by various users of the Cores. The Cores used are listed at the end of each accomplishment.

Energy intake in weight-reduced humans. Almost anyone who has ever lost weight can attest that it is harder to sustain weight loss than to lose weight. Maintenance of a 10% or greater reduced body weight is accompanied by decreases in energy expenditure to levels significantly below what is predicted solely on the basis of weight and body composition changes. This disproportionate decline in energy expenditure would not be sufficient to account for the more than 80% recidivism rate to pre-weight loss levels of body fatness after otherwise successful weight reduction if there were a corresponding reduction in energy intake. In fact, reduced body weight maintenance is accompanied by increased energy intake above that required to maintain reduced weight. The failure to reduce energy intake in response to decreased energy output reflects decreased satiation and perception of how much food is eaten and multiple changes in neuronal signaling in response to food, which conspire with the decline in energy output to keep body energy stores (fat) above a central nervous system (CNS)-defined minimum threshold. Much of this biological opposition to sustained weight loss is mediated by the adipocyte-derived hormone “leptin.” (Body Composition; Molecular Biology)

Effects of experimental weight perturbation on skeletal muscle work efficiency, fuel utilization, and biochemistry in human subjects. Maintenance of a body weight 10% above or below that “customary” for lean or obese individuals results in respective increases or decreases in the energy expended in low levels of physical activity (non-resting energy expenditure). These changes are greater than can be accounted for by the altered body weight or composition, and are due mainly to altered skeletal muscle work efficiency at low levels of power generation. We performed biochemical analysis of vastus lateralis muscle needle biopsy samples to determine whether maintenance of an altered body weight was associated with changes in skeletal muscle histomorphology. We found that the maintenance of a 10% reduced body weight was associated with significant declines in glycolytic (phosphofructokinase, PFK) enzyme activity and, in particular, in the ratio of glycolytic to oxidative (cytochrome c oxidase, COX) enzyme activity without significant changes in the activities of enzymes relevant to mitochondrial density, respiratory chain activity, or fuel transport; or in skeletal muscle fiber type or glycogen stores. The fractional change in the ratio of PFK/COX activity in subjects following weight loss was significantly correlated with changes in the systemic respiratory exchange ratio and measures of mechanical efficiency of skeletal muscle at low workloads (pedaling a bicycle to generate 10 or 25 Watts of power). Thus, predictable changes in systemic skeletal muscle biochemistry accompany the maintenance of an altered body weight and account for a significant portion of the variance in skeletal muscle work efficiency and fuel utilization at reduced body weight. (Body Composition; Adipose Tissue)

In silico mutagenesis: a case study of the melanocortin 4 receptor. The melanocortin 4 receptor (MC4R) is a G-protein-coupled receptor (GPCR) and a key molecule in the regulation

of energy homeostasis. At least 159 substitutions in the coding region of human MC4R (hMC4R) have been described experimentally; more than 80 of those occur naturally, and many have been implicated in obesity. However, assessment of the presumably functionally essential residues remains incomplete. A complete in silico mutagenesis analysis was performed to assess the functional essentiality of all possible non-native point mutants in the entire hMC4R protein (332 residues). SNAP was applied, which is a method for quantifying functional consequences of single amino acid (AA) substitutions, to calculate the effects of all possible substitutions at each position in the hMC4R AA sequence. A mutability score was compiled that reflects the degree to which a particular residue is likely to be functionally important. The same experiment was compiled for a paralogue human melanocortin receptor (hMC1R) and a mouse orthologue (mMC4R) in order to compare computational evaluations of highly related sequences. Three results are most salient: 1) predictions largely agree with the available experimental annotations; 2) this analysis identified several AAs that are likely to be functionally critical, but have not yet been studied experimentally; and 3) the differential analysis of the receptors implicates a number of residues as specifically important to MC4Rs versus other GPCRs, such as hMC1R. (Molecular Biology)

Analysis of 30 genes (355 SNPS) related to energy homeostasis for association with adiposity in European-American and Yup'ik Eskimo populations. Human adiposity is highly heritable, but few of the genes that predispose to obesity in most humans are known. Candidate genes were tested in pathways related to food intake and energy expenditure for association with measures of adiposity. A total of 355 genetic variants were studied in 30 candidate genes in 7 molecular pathways related to obesity in two groups of adult subjects: 1,982 unrelated European Americans living in the New York metropolitan area drawn from the extremes of their body mass index (BMI) distribution and 593 related Yup'ik Eskimos living in rural Alaska characterized for BMI, body composition, waist circumference, and skin fold thickness. Data were analyzed by using a mixed model in conjunction with a false discovery rate (FDR) procedure to correct for multiple testing. After correcting for multiple testing, two single nucleotide polymorphisms (SNPs) in Ghrelin (GHRL) (rs35682 and rs35683) were associated with BMI in the New York European Americans. This association was not replicated in the Yup'ik participants. There was no evidence for gene-x-gene interactions among genes within the same molecular pathway after adjusting for multiple testing via FDR control procedure. In summary, genetic variation in GHRL may have a modest impact on BMI in European Americans. (Molecular Biology)

CNS leptin action modulates immune response and survival in sepsis. Sepsis describes a complex clinical syndrome that results from an infection, setting off a cascade of systemic inflammatory responses that can lead to multiple organ failure and death. Leptin is a 16 kDa adipokine that, among its multiple known effects, is involved in regulating immune function. The NORC has previously demonstrated that leptin deficiency in ob/ob mice leads to higher mortality and more severe organ damage in a standard model of sepsis in mice [cecal ligation and puncture (CLP)]. Moreover, systemic leptin replacement improved the immune response to CLP. Based on the molecular mechanisms of leptin regulation of energy metabolism and reproductive function, it was hypothesized that leptin acts in the CNS to efficiently coordinate peripheral immune defense in sepsis. Results show that leptin signaling in the brain increases survival during sepsis in leptin-deficient as well as in wild-type mice, and that endogenous CNS leptin action is required for an adequate systemic immune response. These findings reveal the existence

of a relevant neuroendocrine control of systemic immune defense and suggest a possible therapeutic potential for leptin analogs in infectious disease. (Molecular Biology; Animal Phenotyping)

Weight loss with naltrexone SR/bupropion SR combination therapy as an adjunct to behavior modification: the COR-BMOD trial. This 56-week, randomized, placebo-controlled trial examined the efficacy and safety of naltrexone plus bupropion as an adjunct to intensive behavior modification (BMOD). A total of 793 participants (BMI = 36.5 +/- 4.2 kg/m²) was randomly assigned in a 1:3 ratio to: (i) placebo + BMOD (N = 202); or (ii) naltrexone sustained-release (SR, 32 mg/day), combined with bupropion SR (360 mg/day) plus BMOD (i.e., NB32 + BMOD; N = 591). Both groups were prescribed an energy-reduced diet and 28 group BMOD sessions. Co-primary end points were percentage change in weight and the proportion of participants who lost greater than or equal to 5% weight at week 56. Efficacy analyses were performed on a modified intent-to-treat population (ITT; i.e., participants with greater than or equal to 1 postbaseline weight while taking study drug [placebo + BMOD, N = 193; NB32 + BMOD, N = 482]). Missing data were replaced with the last observation obtained on study drug. At week 56, weight loss was 5.1 +/- 0.6% with placebo + BMOD versus 9.3 +/- 0.4% with NB32 + BMOD (P < 0.001). A completers analysis revealed weight losses of 7.3 +/- 0.9% (N = 106) versus 11.5 +/- 0.6% (N = 301), respectively (P < 0.001). A third analysis, which included all randomized participants, yielded losses of 4.9 +/- 0.6 versus 7.8 +/- 0.4%, respectively (P < 0.001). Significantly more NB32 + BMOD-treated versus placebo + BMOD-treated participants lost greater than or equal to 5% and greater than or equal to 10% of initial weight, and the former had significantly greater improvements in markers of cardiometabolic disease risk. NB32 + BMOD was generally well tolerated, although associated with more reports of nausea than placebo + BMOD. The present findings support the efficacy of combined naltrexone/bupropion therapy as an adjunct to intensive BMOD for obesity. (Hormone and Metabolites)

Activity patterns of obese adults with type 2 diabetes in the Look AHEAD study. This study describes baseline physical activity (PA) patterns of individuals with type 2 diabetes mellitus enrolled in the multicenter Look AHEAD Study using an objective measure of PA (accelerometry). A total of 2,240 participants (age = 59.0 +/- 6.8 years; BMI = 36.5 +/- 6.0 kg/m) with type 2 diabetes mellitus (T2DM) provided data for this sub-study. Participants were instructed to wear an accelerometer during waking hours over 7 days. Accelerometry data were analyzed to identify periods meeting the criteria of greater than or equal to 3 metabolic equivalents (METs) per minute for at least 10 minutes (moderate to vigorous physical activity, or MVPA) and greater than or equal to 6 METs per minute for at least 10 minutes (vigorous physical activity, or VPA). Self-reported PA was also assessed with a questionnaire. Accelerometry and self-reported PA data were compared across categories of BMI, sex, race, age, fitness, diabetes medication usage, and history of cardiovascular disease. Self-reported PA was lower at higher levels of BMI, was higher in males, was lowest for African American/Black, and was positively associated with fitness. Multivariate analyses for accelerometer-measured MVPA and VPA showed that more PA bouts per day, minutes per bout, METs per minute, and MET-minutes were associated with higher fitness. For MVPA, bouts per day were higher in men, and METs per minute were higher in women. For VPA, bouts per day was positively associated with increasing age and differed by race/ethnicity. (Hormone and Metabolites)

Metabolic changes following a 1-year diet and exercise intervention in patients with type 2 diabetes. The objective was to characterize the relationships among long-term improvements in peripheral insulin sensitivity (glucose disposal rate [GDR]), fasting glucose, and free fatty acids [FFAs]) and concomitant changes in weight and adipose tissue mass and distribution induced by lifestyle intervention in obese individuals with type 2 diabetes. We measured GDR, fasting glucose, and FFAs during a euglycemic clamp and adipose tissue mass and distribution, organ fat, and adipocyte size by dual-energy X-ray absorptiometry (DXA), CT scan, and adipose tissue biopsy in 26 men and 32 women in the Look AHEAD trial before and after 1 year of diet and exercise aimed at weight loss. Results: Weight and fasting glucose decreased significantly ($p < 0.0001$) and significantly more in men than in women (-12% versus -8% and -16% versus -7%, respectively; $p < 0.05$), while FFAs during hyperinsulinemia decreased and GDR increased significantly ($p < 0.00001$) and similarly in both sexes (-53% versus -41% and 63% versus 43%; $p = \text{NS}$). Men achieved a more favorable fat distribution by losing more from upper compared with lower adipose tissue depots and from deeper compared with superficial adipose tissue depots ($p < 0.01$). Decreases in weight and adipose tissue mass predicted improvements in GDR but not in fasting glucose or fasting FFAs; however, decreases in FFAs during hyperinsulinemia significantly determined GDR improvements. Hepatic fat was the only regional fat measure whose change contributed independently to changes in metabolic variables. In conclusion, patients with type 2 diabetes undergoing a 1-year lifestyle intervention had significant improvements in GDR, fasting glucose, FFAs, and adipose tissue distribution. However, changes in overall weight (adipose tissue mass) and hepatic fat were the most important determinants of metabolic improvements. (Hormone and Metabolites; Body Composition; Statistics)

Fat-free mass index: changes and race/ethnic differences in adulthood. Nutritional status is assessed by measuring BMI or percent body fat (%fat). BMI can misclassify persons who carry more weight as fat-free mass and %fat can be misleading in cases of malnutrition or in disease states characterized by wasting of lean tissue. The fat-free mass index (FFMI) is proposed to assess body composition in individuals who have a similar body composition but differ in height, allowing identification of those suffering from malnutrition, or wasting or those who possess a relatively high muscle mass. The purpose was to determine whether the FFMI differs in a group of racially/ethnically diverse adults. This was a cross-sectional design. Subjects were a multi-ethnic sample (Caucasian, CA; African American, AA; Hispanic, HIS; and Asian, AS) of 1,339 healthy males ($n = 480$) and females ($n = 859$) ranging in age from 18 year to 110 years. Total body fat, total fat-free mass, and bone mineral density were estimated using DXA. Researchers found that FFMI differed among the four ethnic groups ($p \leq 0.05$) for both genders. A curvilinear relationship was found between age and FFMI for both genders although the coefficients in the quadratic model differed between genders ($p \leq 0.001$), indicating the rate of change in FFMI differed between genders. The estimated turning point at which FFMI started to decline was in the mid 20s for male participants and the mid 40s for female participants. An age-x-gender interaction was found such that the rate of decline was greater in male participants than female participants ($p \leq 0.001$). For both genders, FFMI was greatest in AA and the least in AS ($p \leq 0.001$). There was no significant interaction between race and age or age² ($p = 0.06$). However, male participants consistently had a greater FFMI than female participants ($p \leq 0.001$). These findings have clinical implications for identifying individuals who may not be recognized as being malnourished based on their BMI or %fat but whose fat-free mass corrected for height is relatively low.

Greater lean tissue and skeletal muscle mass are associated with higher bone mineral content in children. The relationship of skeletal muscle mass with bone mineral content was compared in an ethnically diverse group of 6-year-old to 18-year-old boys and girls. A total of 175 healthy children (103 boys, 72 girls) had assessments of body mass, height, and Tanner stage. Whole body bone mineral content, non-bone lean body mass (nbLBM), skeletal muscle mass, and fat mass were assessed using DXA. Muscle mass was estimated from an equation using appendicular lean soft tissue measured by DXA, weight, and height. Estimates of skeletal muscle mass and adipose tissue were also assessed by whole body multi-slice MRI. Linear regression was used to determine whether skeletal muscle mass assessed by DXA or by MRI were better predictors of bone mineral content compared with nbLBM after adjusting for sex, age, race or ethnicity, and Tanner stage. Greater skeletal muscle mass was associated with greater bone mineral content ($p < 0.001$). The skeletal muscle mass assessed by MRI provided a better fitting regression model (determined by R^2 statistic) compared with assessment by DXA for predicting bone mineral content. The proportion of skeletal muscle mass in nbLBM was significantly associated with greater bone mineral content adjusted for total nbLBM. This study is among the first to describe and compare the relationship of skeletal muscle to bone using both MRI and DXA estimates. The results demonstrate that the use of MRI provides a modestly better-fitting model for the relationship of skeletal muscle to bone compared with DXA. Skeletal muscle had an impact on bone mineral content independent of total non-bone lean body mass. In addition, Hispanics had greater bone mineral content compared to other race and ethnic groups after adjusting for sex, age, adipose tissue, skeletal muscle mass, and height.

Brain and high metabolic rate organ mass: contributions to resting energy expenditure beyond fat-free mass. The degree to which inter-individual variation in the mass of select high metabolic rate organs (HMROs) mediates variability in resting energy expenditure (REE) is unknown. The objective was to investigate how much REE variability is explained by differences in HMRO mass in adults and whether age, sex, and race independently predict REE after adjustment for HMRO. A cross-sectional evaluation of 55 women [30 African Americans aged 48.7 \pm 22.2 years (mean \pm SD) and 25 whites aged 46.4 \pm 17.7 years] and 32 men (8 African Americans aged 34.3 \pm 18.2 years and 24 whites aged 51.3 \pm 20.6 years) was conducted. Liver, kidney, spleen, heart, and brain masses were measured by MRI, and fat and fat-free mass (FFM) were measured by DXA. REE was measured by indirect calorimetry. REE estimated from age ($p = 0.001$), race ($p = 0.006$), sex ($p = 0.31$), fat ($p = 0.001$), and FFM ($p < 0.001$) accounted for 70% (adjusted (2)) of the variability in REE. The addition of trunk HMRO ($p = 0.001$) and brain ($p = 0.006$) to the model increased the explained variance to 75% and rendered the contributions of age, sex, and race statistically non-significant, whereas fat and FFM continued to make significant contributions (both $p < 0.05$). The addition of brain to the model rendered the intercept (69 kcal \cdot kg⁻¹ \cdot d⁻¹) consistent with zero, which indicated zero REE for zero body mass. In conclusion, relatively small inter-individual variation in HMRO mass significantly affects REE and reduces the role of age, race, and sex in explaining REE. Decreases in REE with increasing age may be partly related to age-associated changes in the relative size of FFM components.

Elderly Mexicans have less muscle and greater total and truncal fat compared to African-Americans and Whites with the same BMI. How body composition, specifically skeletal muscle mass, compares in Mexican elderly to other ethnic groups has not previously been reported. We tested the hypothesis that older adults from Northwest Mexico (Mex) would have

similar total appendicular skeletal muscle (TASM) compared with New York dwelling Whites (W) and African Americans (AA). Two hundred and eighty nine Mex (135 males and 154 females), 166 AA (36 males and 130 females), and 229 W (64 males and 165 females), 60 years to 98 years old, were assessed. Total and regional fat and lean tissues were measured by whole-body DXA where TASM is the sum of arm and leg bone-free and fat-free lean tissue. Differences in TASM were tested by analysis of covariance, with age, height, and BMI as covariates. TASM adjusted for ethnicity, age, height, and BMI were 22.6 +/- 0.2 kg and 17.8 +/- 0.1 kg for males and females, respectively ($p < 0.001$). Among males with similar age, height, and BMI, Mex had less TASM compared with AA and W ($p < 0.001$). Total body fat and truncal fat were higher ($p < 0.001$) and FFM lower ($p < 0.001$) in Mex compared to both AA and W males after adjusting for age and BMI. Among females, Mex had higher total and truncal fat ($p < 0.001$) after adjusting for age and BMI, and significantly lower TASM ($p < 0.001$) after adjusting for age, height, and BMI compared to AA and W females. Elderly Mex have a different body composition compared with AA and W of a similar BMI and age. Mex have significantly less TASM with greater total and truncal fat. In the long term, Mex elderly may be at greater risk for sarcopenic obesity compared to other ethnic groups. (Body Composition; Statistics)

Marine omega-3 fatty acid intake: associations with cardiometabolic risk and response to weight loss intervention in the Look AHEAD (Action for Health in Diabetes) study. The purpose of the study was to examine the usual marine omega-3 fatty acid (mO-3FA) intake in individuals with diabetes; its association with adiposity, lipid, and glucose control; and its changes with behavioral lifestyle intervention for weight loss. Cross-sectional and 1-year longitudinal analyses were performed on 2,397 Look AHEAD (Action for Health in Diabetes) participants. Look AHEAD is a cardiovascular outcome trial evaluating the effects of intensive lifestyle intervention for weight loss in overweight/obese subjects with type 2 diabetes. Baseline mO-3FA intake was 162 +/- 138 mg/day. It was inversely associated with triglycerides ($\beta = -0.41$, $p < 0.001$) and weakly associated with high-density lipoproteins ($\beta = 4.14$, $p = 0.050$), after multiple covariate adjustment. One-year mO-3FA and fried/sandwich fish intake decreased with intensive lifestyle intervention ($p < 0.001$). Intake of mO-3FA in Look AHEAD participants was low but associated favorably with lipids. These results encourage investigation into the potential benefits of increasing mO-3FA intake in lifestyle interventions for weight loss in individuals with diabetes. (Hormone and Metabolites)

A randomized study on the effect of weight loss on obstructive sleep apnea among obese patients with type 2 diabetes: the Sleep AHEAD study. The belief that weight loss improves obstructive sleep apnea (OSA) has limited empirical support. The purpose of this four-center study was to assess the effects of weight loss on OSA during a 1-year period. The study included 264 participants with type 2 diabetes and a mean (SD) age of 61.2 (6.5) years, weight of 102.4 (18.3) kg, BMI (calculated as weight in kilograms divided by height in meters squared) of 36.7 (5.7), and an apnea-hypopnea index (AHI) of 23.2 (16.5) events per hour. The participants were randomly assigned to either a behavioral weight loss program developed specifically for obese patients with type 2 diabetes (intensive lifestyle intervention [ILI]) or three group sessions related to effective diabetes management (diabetes support and education [DSE]). The ILI participants lost more weight at 1 year than did DSE participants (10.8 kg versus 0.6 kg; $p < .001$). Relative to the DSE group, the ILI intervention was associated with an adjusted (SE) decrease in AHI of 9.7 (2.0) events per hour ($p < .001$). At 1 year, more than three times as many participants in the ILI group than in the DSE group had total remission of their OSA, and the prevalence of

severe OSA among ILI participants was half that of the DSE group. Initial AHI and weight loss were the strongest predictors of changes in AHI at 1 year ($p < .01$). Participants with a weight loss of 10 kg or more had the greatest reductions in AHI. Physicians and their patients can expect that weight loss will result in significant and clinically relevant improvements in OSA among obese patients with type 2 diabetes. (Statistics)

Effects of selective modulation of the central melanocortin-3-receptor on food intake and hypothalamic proopiomelanocortin (POMC) expression. Hypothalamic POMC neurons regulate energy balance via interactions with brain melanocortin receptors (MC-Rs). POMC neurons express the MC3-R, which can function as an inhibitory autoreceptor in vitro. We now demonstrate that central activation of MC3-R with intracerebroventricular (ICV) infusion of the specific MC3-R agonist, [D-Trp(8)]-gamma-MSH, transiently suppresses hypothalamic POMC expression and stimulates food intake in rats. Conversely, ICV infusion of a low dose of a selective MC3-R antagonist causes a transient decrease in feeding and weight gain. These data support a functional inhibitory role for the MC3-R on POMC neurons that leads to changes in food intake. (Molecular Biology)

Transgenic melanocyte stimulating hormone (MSH) overexpression attenuates the metabolic effects of a high-fat diet. To determine whether long-term melanocortinergic activation can attenuate the metabolic effects of a high-fat diet (HFD), mice overexpressing an NH(2)-terminal POMC transgene that includes alpha- and gamma(3)-MSH were studied on either a 10% low-fat diet (LFD) or 45% HFD. Weight gain was modestly reduced in transgenic (Tg-MSH) male and female mice versus wild-type (WT) on HFD ($p < 0.05$) but not LFD. Substantial reductions in body fat percentage were found in both male and female Tg-MSH mice on LFD ($p < 0.05$) and were more pronounced on HFD ($p < 0.001$). These changes occurred in the absence of significant feeding differences in most groups, consistent with effects of Tg-MSH on energy expenditure and partitioning. This is supported by indirect calorimetry studies demonstrating higher resting oxygen consumption and lower respiratory quotient (RQ) in Tg-MSH mice on the HFD. Tg-MSH mice had lower fasting insulin levels and improved glucose tolerance on both diets. Histological and biochemical analyses revealed that hepatic fat accumulation was markedly reduced in Tg-MSH mice on the HFD. Tg-MSH also attenuated the increase in corticosterone induced by the HFD. Higher levels of Agouti Related Protein (AGRP) mRNA, which might counteract effects of the transgene, were measured in Tg-MSH mice on LFD ($p = 0.02$) but not HFD. These data show that long-term melanocortin activation reduces body weight, adiposity, and hepatic fat accumulation and improves glucose metabolism, particularly in the setting of diet-induced obesity. Our results suggest that long-term melanocortinergic activation could serve as a potential strategy for the treatment of obesity and its deleterious metabolic consequences. (Molecular Biology; Animal Phenotyping)

Rise of oxyntomodulin in response to oral glucose after gastric bypass surgery in patients with type 2 diabetes. The mechanisms by which Roux-en-Y gastric bypass surgery (GBP) results in sustained weight loss and remission of type 2 diabetes are not fully understood. Objective: We hypothesized that the anorexic hormone oxyntomodulin (OXM) might contribute to the marked weight reduction and the rapid improvement in glucose metabolism observed in morbidly obese diabetic patients after GBP. Twenty obese women with type 2 diabetes were studied before and 1 month after GBP ($n = 10$) or after a diet-induced equivalent weight loss ($n = 10$). Patients from both groups were matched for age, body weight, BMI, and diabetes

duration and control. OXM concentrations were measured during a 50-gram oral glucose challenge before and after weight loss. At baseline, OXM levels (fasting and stimulated values) were indistinguishable between the GBP and the diet group. However, OXM levels rose remarkably in response to an oral glucose load more than two-fold (peak, 5.25 +/- 1.31 to 13.8 +/- 16.2 pmol/liter; p=0.025) after GBP but not after diet. The peak of OXM after glucose was significantly correlated with glucagon-like peptide-1 and peptide YY3-36. These data suggest that the observed changes in OXM primarily occur in response to GBP and not as a consequence of weight loss. These changes were observed early after surgery and occurred in parallel with previously reported increases in incretins and peptide YY. We speculate that the combination of gut hormone changes is essential for the improved glucose homeostasis and may partially explain the success of this surgery on diabetes resolution and weight loss. (Ingestive Behavior; Hormone and Metabolites)

Effect of weight loss by diet or gastric bypass surgery on peptide YY3-36 levels. The increased PYY3-36 levels after GBP may be involved in the magnitude and the sustainability of weight loss after surgery. The effect of an equivalent weight loss, by GBP or by diet, was examined with regard to peptide YY3-36 (PYY3-36), ghrelin, and leptin levels and to determine the effect of diabetes status on PYY3-36 levels. Of the 30 morbidly obese women who participated in the study, 21 had type 2 diabetes mellitus, and were studied before and after equivalent weight loss of 10 kg by either GBP (n=11) or by diet (n=10). PYY3-36 levels were higher in obese diabetic as compared with non-diabetic individuals (64.1 +/- 34.4 pg/mL vs. 39.9 +/- 21.1 pg/mL; p<0.05). PYY3-36 levels increased markedly in response to oral glucose after GBP (peak: 72.3 +/- 20.5 pg/mL-132.7 +/- 49.7 pg/mL; p<0.001; AUC0-180: 51.5 +/- 23.3 pg/mL x min-91.1 +/- 32.2 pg/mL x min p<0.001), but not after diet (peak: 85.5 +/- 51.9 pg/mL-84.8 +/- 41.13 pg/mL; p=NS; AUC0-180: 68.3 +/- 38.5 pg/mL x min-61.1 +/- 42.2 pg/mL.min p=NS). Fasting ghrelin levels increased after diet (425 +/- 91 pg/mL-519 +/- 105 pg/mL; p<0.05), but did not change after GBP (506 +/- 121 pg/mL-482 +/- 196 pg/mL; p=NS). In conclusion, diabetes status seems to be a determinant of PYY3-36 levels. GBP, but not diet-induced weight loss, resulted in markedly increased glucose-stimulated PYY3-36 levels. The increase in stimulated PYY3-36 levels after GBP is likely a result of the surgery rather than a secondary outcome of weight loss. Changes in PYY3-36 levels and ghrelin could contribute to the success of GBP in sustaining weight loss. (Hormone and Metabolites; Ingestive Behavior)

Prospective study of gut hormone and metabolic changes after adjustable gastric banding and Roux-en-Y gastric bypass. The objective of this study was to quantify hormones that regulate energy and glucose homeostasis to establish possible mechanisms for the greater efficacy of Roux-en-Y gastric bypass (RYGB) compared with laparoscopic adjustable gastric banding (LAGB) in achieving weight loss and improved insulin sensitivity. A longitudinal study of patients undergoing LAGB (n=15) and RYGB (n=28) was undertaken before surgery and at 2, 12, 26, and 52 weeks after surgery. Fasting blood samples were drawn at each visit. Postprandial blood samples were also obtained before surgery and at 26 and 52 weeks. Samples were assayed for PYY, ghrelin, glucagon-like peptide-1 (GLP-1), glucose, insulin, leptin, thyrotropic hormone, free T(4) and free T(3). At 1 year there was greater weight loss in RYGB compared with LAGB patients (30% versus 15%), but final body mass index was similar (34 versus 33 kg/m(-2)). At week 52, area under the curve (AUC) for PYY in RYGB subjects was greater than LAGB (p<0.01). GLP-1 levels at 30 minutes after meal were threefold greater after RYGB compared with LAGB (p<0.001). Conversely, ghrelin AUC increased after LAGB at week 52 (p<0.05) but

tended to decrease after RYGB. Fasting glucose, insulin, leptin, and homeostasis model of assessment (HOMA-IR) decreased in both groups over time but were significantly lower at week 52 after RYGB compared with LAGB. The change in leptin correlated significantly with weight loss in LAGB ($r=0.86$) and RYGB ($r=0.77$); however, HOMA-IR correlated significantly with weight loss only in LAGB ($r=0.78$) and not RYGB ($r=0.15$). There was a significant decrease in free T(3) ($p<0.01$) after RYGB. In summary, differences in levels of gut hormones may play a role in promoting greater weight loss and insulin sensitivity after RYGB compared with LAGB; however, weight loss may be limited by decreases in free T(3) and leptin. (Hormone and Metabolites; Statistics)

Association of body mass and brain activation during gastric distention: implications for obesity. Gastric distention (GD), as it occurs during meal ingestion, signals a full stomach and it is one of the key mechanisms controlling food intake. Previous studies on GD showed lower activation of the amygdala for subjects with higher BMI. Since obese subjects have dopaminergic deficits that correlate negatively with BMI and the amygdala is innervated by dopamine neurons, we hypothesized that BMI would correlate negatively with activation not just in the amygdala but also in other dopaminergic brain regions (midbrain and hypothalamus). fMRI was used to evaluate brain activation during GD in 24 healthy subjects with a BMI range of 20 to 39 kg/m². Using multiple regression and cross-correlation analyses based on a family-wise error corrected threshold $p=0.05$, we showed that during slow GD to maximum volumes of 500 ml and 700 ml, subjects with increased BMI had increased activation in cerebellum and left posterior insula, and decreased activation of dopaminergic (amygdala, midbrain, hypothalamus, thalamus) and serotonergic (pons) brain regions and anterior insula, regions that were functionally interconnected with one another. The negative correlation between BMI and blood-oxygenation level dependent (BOLD)-fMRI responses to gastric distention in dopaminergic (midbrain, hypothalamus, amygdala, thalamus) and serotonergic (pons) brain regions is consistent with disruption of dopaminergic and serotonergic signaling in obesity. In contrast, the positive correlation between BMI and BOLD-fMRI responses in posterior insula and cerebellum suggests an opposing mechanism that promotes food intake in obese subjects that may underlie their ability to consume at once large food volumes despite increasing gastric distention. (Ingestive Behavior; Statistics)

Sex differences in the effects of inherited bitter thiourea sensitivity on body weight in 4- to 6-year-old children. Previous studies have shown that inherited taste blindness to bitter compounds like 6-n-propylthiouracil (PROP) may be a risk factor for obesity, but this literature has been highly controversial. The objectives of this study were (i) to confirm findings that show an interaction between PROP status and sex on BMI z-score and (ii) to determine if sex also interacts with variations in TAS2R38 (phenylthiocarbamide [PTC] genotype) to influence weight status in 4-year-olds to 6-year-olds. Also, we tested whether non-taster children consumed more fat and total energy at laboratory-based meals. Seventy-two ethnically diverse children who ranged in weight status were classified as tasters ($N=52$) or non-tasters ($N=20$) using a standard PROP screening solution. Anthropometric measures were taken and, at the end of each visit, children ate ad libitum from test meals intended for exploratory purposes. Genomic DNA was extracted from saliva and alleles and TAS2R38 were genotyped for A49P polymorphisms. In 75.8% of children, PTC genotype predicted PROP phenotype, whereas in 24.4%, genotype did not predict phenotype. PROP non-taster males had higher BMI z-scores than taster males and females in both groups ($p<0.05$), but due to a three-way interaction between PROP phenotype,

TAS2R38 genotype, and sex, this relationship was only true for children who were homozygous for the bitter-insensitive allele ($p < 0.0005$). There were no differences in test-meal intake as a function of PROP phenotype or TAS2R38 genotype. These results suggest that the TAS2R38 variation, the PROP phenotype, and sex interact to impact obesity risk in children. Future studies are being done to determine how this trait influences energy balance. (Ingestive Behavior; Statistics)

The development of satiation in bulimia nervosa. Bulimia nervosa (BN) is characterized by the recurrent consumption of excessive amounts of food (binge eating) followed by inappropriate compensatory behaviors. A leading hypothesis is that the persistence of BN may be due, in part, to a disturbance in the development of satiation. Because patients with BN consume larger meals than controls, previous studies have not been able to directly compare the development of satiation. In order to address this problem, subjects consumed large meals of predetermined size without knowing when they would be stopped. Twenty-one women with BN and 13 control women participated in a study in which they rated hunger and fullness during the course of a 975 g liquid meal eaten from an opaque reservoir. Subjects' ratings were obtained after each 75 g increment of consumption. There were no statistically significant differences between the two groups in the mean ratings of hunger or of fullness before, after, or during the meal. Individuals with BN consumed the meal more rapidly than control participants. These results suggest that, when individuals with BN are not instructed to binge eat and do not control meal size, they do not manifest a disturbance in reported satiation over the course of a large liquid meal. (Ingestive Behavior; Statistics)

Differential effects of hypothalamic long chain fatty acid infusions on suppression of hepatic glucose production. The purpose of this research was to investigate whether the direct bilateral infusion of the mono-unsaturated fatty acid (MUFA) oleic acid (OA) within the medio-basal hypothalamus (MBH) is sufficient to reproduce the effect of administration of OA (30 nmoles) in the third cerebral ventricle, which inhibits glucose production (GP) in rats. We used the pancreatic basal insulin clamp technique (plasma insulin ~ 20 $\mu\text{U}/\text{ml}$) in combination with tracer-dilution methodology to compare the effect of MBH OA on GP to that of a saturated fatty acid (SFA), palmitic acid (PA), and a polyunsaturated fatty acid, linoleic acid (LA). The MBH infusion of 200 but not 40 pmoles of OA was sufficient to markedly inhibit GP (by 61% from 12.6 ± 0.6 to 5.1 ± 1.6 $\text{mg}/\text{kg}\cdot\text{min}$) such that exogenous glucose had to be infused at the rate of 6.0 ± 1.2 $\text{mg}/\text{kg}\cdot\text{min}$ to prevent hypoglycemia. MBH infusion of PA also caused a significant decrease in GP, but only at a total dose of 4 nmoles (GP 5.8 ± 1.6 $\text{mg}/\text{kg}\cdot\text{min}$). Finally, MBH LA at a total dose of 0.2 and 4 nmoles failed to modify GP compared to rats receiving MBH vehicle. In conclusion, increased availability of OA within the MBH is sufficient to markedly inhibit GP. LA does not share the effect of OA, while PA can reproduce the potent effect of OA on GP, but only at a higher dose. It remains to be determined whether SFAs need to be converted to MUFAs in order to exert this effect or if they activate a separate signaling pathway to inhibit GP. (Animal Phenotyping; Hormones and Metabolites)

An intrinsic gut leptin-melanocortin pathway modulates intestinal microsomal triglyceride transfer protein (MTP) and lipid absorption. Fat is delivered to tissues by apoB-containing lipoproteins synthesized in the liver and intestine with the help of an intracellular chaperone, microsomal triglyceride transfer protein (MTP). Leptin, a hormone secreted by adipose tissue, acts in the brain and on peripheral tissues to regulate fat storage and metabolism. Our aim was to

identify the role of leptin signaling in MTP regulation and lipid absorption using several mouse models deficient in leptin receptor (LEPR) signaling and downstream effectors. Mice with spontaneous LEPR B mutations or targeted ablation of LEPR B in proopiomelanocortin (POMC) or agouti gene related peptide (AGRP) expressing cells had increased triglyceride in plasma, liver, and intestine. Furthermore, melanocortin 4 receptor (MC4R) knockout mice expressed a similar triglyceride phenotype, suggesting that leptin might regulate intestinal MTP expression through the melanocortin pathway. Mechanistic studies revealed that the accumulation of triglyceride in the intestine might be secondary to decreased expression of MTP and lipid absorption in these mice. Surgical and chemical blockade of vagal efferent outflow to the intestine in wild-type mice failed to alter the triglyceride phenotype, demonstrating that central neural control mechanisms were likely not involved in the observed regulation of intestinal MTP. Instead, we found that enterocytes express LEPR, POMC, AGRP, and MC4R. We propose that a peripheral, local gut signaling mechanism involving LEPR B and MC4R regulates intestinal MTP and controls intestinal lipid absorption. (Animal Phenotyping; Molecular Biology)

Hypothalamic leptin signaling regulates hepatic insulin sensitivity via a neurocircuit involving the vagus nerve. Recent evidence suggests that hormones such as insulin and leptin act in the hypothalamus to regulate energy balance and glucose metabolism. In leptin receptor-deficient Koletsky (fa(k)/fa(k)) rats, adenovirally induced expression of leptin receptors in the area of the hypothalamic arcuate nucleus improved peripheral insulin sensitivity via enhanced suppression of hepatic glucose production, with no change of insulin-stimulated glucose uptake or disposal. This effect was associated with increased insulin signal transduction via phosphatidylinositol-3-OH kinase (as measured by pY-insulin receptor substrate-1 and pS-PKB/Akt) in liver, but not skeletal muscle, and with reduced hepatic expression of the gluconeogenic genes, glucose-6-phosphatase and phosphoenolpyruvate kinase. Moreover, the beneficial effects of hypothalamic leptin signaling on hepatic insulin sensitivity were blocked by selective hepatic vagotomy. We conclude that hypothalamic leptin action increases peripheral insulin sensitivity primarily via effects on the liver and that the mechanism underlying this effect is dependent on the hepatic branch of the vagus nerve. (Animal Phenotyping; Adipose Tissue)

Mediobasal hypothalamic leucine sensing regulates food intake through activation of a hypothalamus-brainstem circuit. In response to nutrient stimuli, the mediobasal hypothalamus (MBH) drives multiple neuroendocrine and behavioral mechanisms to regulate energy balance. While central leucine reduces food intake and body weight, the specific neuro-anatomical sites of leucine sensing, downstream neural substrates, and neurochemical effectors involved in this regulation remain largely unknown. Here it is demonstrated that MBH leucine engages a neural energy regulatory circuit by stimulating POMC neurons of the MBH, oxytocin neurons of the paraventricular hypothalamus, and neurons within the brainstem nucleus of the solitary tract to acutely suppress food intake by reducing meal size. Central p70 S6 kinase and Erk1/2 pathways are identified as intracellular effectors required for this response. Activation of endogenous leucine intracellular metabolism produced longer-term reductions in meal number. These data identify a novel, specific hypothalamus-brainstem circuit that links amino acid availability and nutrient sensing to the control of food intake. (Adipose Tissue)

C-C chemokine receptor 2 (CCR2) regulates the hepatic recruitment of myeloid cells that promote obesity-induced hepatic steatosis. Obesity induces a program of systemic inflammation that is implicated in the development of many of its clinical sequelae. Hepatic

inflammation is a feature of obesity-induced liver disease, and our previous studies demonstrated reduced hepatic steatosis in obese mice deficient in the CCR2 that regulates myeloid cell recruitment. This suggests that a myeloid cell population is recruited to the liver in obesity and contributes to nonalcoholic fatty liver disease. Fluorescence-activated cell sorting was used to measure hepatic leukocyte populations in genetic and diet forms of murine obesity. In vivo models were characterized that increase and decrease an obesity-regulated CCR2-expressing population of hepatic leukocytes. Finally, using an in vitro co-culture system, the ability of these cells to modulate a hepatocyte program of lipid metabolism was measured. It is demonstrated that obesity activates hepatocyte expression of C-C chemokine ligand 2 (CCL2/MCP-1) leading to hepatic recruitment of CCR2(+) myeloid cells that promote hepatosteatosis. The quantity of these cells correlates with body mass and in obese mice represents the second largest immune cell population in the liver. Hepatic expression of CCL2 increases their recruitment and in the presence of dietary fat induces hepatosteatosis. These cells activate hepatic transcription of genes responsible for fatty acid esterification and steatosis. In conclusion, obesity induces hepatic recruitment of a myeloid cell population that promotes hepatocyte lipid storage. These findings demonstrate that recruitment of myeloid cells to metabolic tissues is a common feature of obesity, not limited to adipose tissue. (Adipose Tissue)

Macrophage content in subcutaneous adipose tissue: associations with adiposity, age, inflammatory markers, and whole-body insulin action in healthy Pima Indians. In severely obese individuals and patients with diabetes, accumulation and activation of macrophages in adipose tissue has been implicated in the development of obesity-associated complications, including insulin resistance. We sought to determine whether in a healthy population, adiposity, sex, age, or insulin action is associated with adipose tissue macrophage content (ATMc) and/or markers of macrophage activation. Subcutaneous ATMc from young adult Pima Indians with a wide range of adiposity (13% to 46% body fat, by whole-body DXA) and insulin action (glucose disposal rate 1.6 mg/kg to 9 mg/kg estimated metabolic body size/min, by glucose clamp) were measured. We also measured expression in adipose tissue of factors implicated in macrophage recruitment and activation to determine any association with ATMc and insulin action. ATMc, as assessed by immunohistochemistry (Mphi) and by macrophage-specific gene expression (CD68, CD11b, and CSF1R), correlated with percent body fat, age, and female sex. Gene expression of CD68, CD11b, and CSF1R but not Mphi was correlated negatively with glucose disposal rate but not after adjustment for percent body fat, age, and sex. However, adipose tissue expression of plasminogen activator inhibitor type-1 (PAI-1) and CD11 antigen-like family member C (CD11c), markers produced by macrophages, were negatively correlated with adjusted glucose disposal rate ($r = -0.28$, $p=0.05$ and $r = -0.31$, $p=0.03$). In summary, ATMc is correlated with age and adiposity but not with insulin action independent of adiposity in healthy human subjects. However, PAI-1 and CD11c expression are independent predictors of insulin action, indicating a possible role for adipose tissue macrophage activation. (Adipose Tissue)

Specific Accomplishments

Women's Health

Investigators are working in various areas related to women's health: the effect of weight loss on body composition, the effect of weight loss on calcium loss, the effect of pituitary hormones on food intake regulation, and the effect of body fat distribution on insulin resistance.

Minority Health

The NY NORC is a site for both the **Diabetes Prevention Trial Outcomes Study** and the **Look AHEAD** trial, each of which has a substantial over-representation of minority subjects, so that it will be possible to analyze minority groups separately. The NY NORC is pursuing a systematic study of the metabolic differences in African American and white women in relation to body fatness and body fat distribution. Differences between African American and white women have been found, and are being pursued (Metabolic Differences in Fat Oxidation between Obese AA and W Women). The **Rosetta Study** has followed minority children through the various Tanner stages for a comparative evaluation of body composition changes in white, African American, Asian, and Hispanic children and is now complete.

A study is being conducted in a group of junior high school children in New York City. A large number of the children are from minorities. This study is examining the prevalence of prediabetic risk factors and the response of the risk factors to an exercise, health, and nutrition education program and will be evaluating its effectiveness. This study is being supported by a large grant from the Academy for Medical Development and Collaboration.

Obesity

All of the investigation at NY NORC is focused on research on this condition. The research is at the basic, animal, and human clinical translational levels. Because of the expertise of the investigators at the Center, we also conduct many clinical trials of new drugs being developed for weight loss.

AIDS

The NY NORC is studying the abnormal fat distribution (lipoatrophy) that comes with long-time HIV infection and/or its treatment. The metabolic health risks of this condition are being measured in cross-sectional and longitudinal studies.

Health Promotion/Disease Prevention

Diabetes Prevention Program Outcomes Study (DPPOS). The existence and available resources of the NY NORC were helpful in obtaining a grant for SLRHC to be one of the Centers in the NIH DPPOS. The purpose of the initial DPP was to determine whether lifestyle change (diet and exercise) and/or drug therapy (metformin) can prevent or delay the onset of type 2 diabetes in individuals with impaired glucose tolerance who are at high risk. This was found to be so. The Data Safety Monitoring Board terminated the study early because both the lifestyle and drug arms significantly decreased conversion to diabetes as compared to the usual

care placebo control. The trial is continuing for another 10 years as the DPPOS to obtain further cardiovascular and other secondary endpoint results. Dr. Pi-Sunyer is the principal investigator.

The Look AHEAD Trial. The existence and available resources of the NY NORC were helpful in obtaining a grant for SLRHC to be one of the Centers in the NIH Look AHEAD Trial. Dr. Pi-Sunyer is the principal investigator as well as national co-Chair of the study. Look AHEAD is a multicenter, randomized clinical trial designed to determine whether interventions for producing sustained weight loss in obese individuals with type 2 diabetes will improve overall health. It will also determine how the benefits and risks of interventions designed to produce weight loss compare with the benefits and risks related to treatment of obesity-related comorbid conditions in the absence of weight-loss interventions.

Bari 2D Trial. In a similar manner, the existence and resources of the NY NORC were important in our being a site for the Bari 2D trial. This NIH-supported trial was designed to test two hypotheses: (1) coronary revascularization hypothesis: that a strategy of initial elective revascularization of choice (surgical or catheter-based) combined with aggressive medical therapy results in lower 5-year mortality compared to a strategy of aggressive medical therapy alone; and (2) a method of glycemic control hypothesis: that with a target of HbA1c level of lower than 7.0%, a strategy of hyperglycemia management directed at insulin sensitization, results in lower 5-year mortality compared to a strategy of insulin provision. Dr. Jeanine Albu has been the principal investigator at this site. The study has been completed and results were published in the *New England Journal of Medicine* in 2009.

Longitudinal Assessment of Bariatric Surgery (LABS) Study: This study of the effects of bariatric surgery is being conducted longitudinally at a number of sites. One clinical site is at Columbia under Dr. Paul Berk.

Educational Activities/Accomplishments

Pilot and Feasibility (P/F) Program. The NY NORC supports a pilot and feasibility grant research program of up to \$25,000 annually per investigator in obesity. Three to four P/F grant awards are given out each year. The program has been very successful in helping young investigators begin their careers in obesity research, and also in bringing older, established investigators into the field.

Seminars and Visiting Scientist Program. The NY NORC has three weekly research seminar series, one each at SLRHC, CUMC, and AECOM; a monthly seminar on ingestive behavior sponsored by the Columbia University Seminars for all, and two mini-symposia per year. A journal club meets weekly. The NY NORC also has a visiting scientist program. This year visiting scientists came from Japan, South Korea, Spain, Taiwan, and the United Kingdom, staying for a minimum of 1 year.

Postdoctoral Training Program. The NY NORC has had an NIH-sponsored T32 postdoctoral training program in obesity with five slots for many years. It is now up for competitive renewal. The Institute of Human Nutrition at Columbia, of which the NY NORC is a part, has another predoctoral training T32 grant in nutrition. The NY NORC has also recently received a

postdoctoral salary support grants of 2 years from the New York Empire State Foundation, given to some of our promising young M.D. investigators.

Professional Education. The NY NORC has been one of the eight sites of the Centers of Obesity Research and Education (CORE), whose mission has been to educate physicians and other health professionals in the management of obesity. The NY NORC has provided half-day workshops for both residents and practicing physicians throughout the year. These have been held both at the NY NORC site and at other sites in the New York City metropolitan area and beyond. Workshops have also been held in nearby locales. Evaluations of these workshops have been outstanding. With this program, we have reached more than 300 physicians a year. We have funded this program with grants from the Mannix Foundation and the Josiah Macy Foundation for the last 5 years and are now trying to obtain further funding to continue the program.

Nutrition Courses. The faculty who are members of the Institute of Human Nutrition at Columbia participate in a required one-semester course for first-year medical students. Further, the NY NORC participates in a one-semester course in clinical nutrition and is specifically in charge of a one-semester course in obesity for the Institute of Human Nutrition. The faculty also participates in the doctoral program courses in nutritional biochemistry.

Other Nutrition Initiatives. The NY NORC welcomes students from nutrition programs at Columbia's Institute of Human Nutrition and Columbia Teachers' College. The NY NORC provides teaching and training in clinical and basic nutrition to residents and fellows in medicine. In addition, the faculty offers research electives in nutrition and obesity for medical students at the fourth-year level. Medical students from the Columbia College of Physicians and Surgeons and other medical schools can rotate through the program electively for 1 month.

Continuing and Community Education. NY NORC investigators participate in numerous continuing education programs for physicians, other health care professionals, and research scientists. These include local, national, and international programs. NY NORC investigators also participate in community education programs organized by the hospital, the university, voluntary agencies, and other New York institutions.

Website. The NY NORC has a website (<http://www.NYORC.org>) on which information about the Center, its Core Laboratories, and its research and educational activities are posted.

Media. NY NORC investigators are frequently in demand by media, particularly so because they are based in New York City, the media capital of the country. The NY NORC strives to oblige, and considers it a duty to help educate the public on matters of obesity and nutrition in general.

Benefits and Interactions Resulting from the Existence of the NY NORC

The NY NORC provides expertise for the treatment and investigation of obesity and eating disorders. The NY NORC has been instrumental in organizing an active program in obesity surgery both at SLRHC and CUMC. Active research on bariatric surgery is ongoing. It has also helped to organize an active and successful sleep laboratory and a Weight Management Center.

The presence of the NY NORC has been important in focusing attention on both basic and clinical research in the area of obesity. It has fostered collaboration among investigators. It is because of this interest and collaboration that advances in the genetics of obesity, ingestive behavior, body composition, and inflammation have occurred. The NY NORC imparts knowledge and biological samples to other investigators both within and outside the Center.

The different but complementary interests of the various Cores at the three institutions have put the NY NORC in a strong position of advocacy and consultation in the area of obesity, weight loss, and eating disorders. There is a large commitment on the part of the faculty of the NY NORC to train new scientists for careers in obesity research.

In addition, the NY NORC investigators use the CTSA at CUMC and the satellite GTSA unit at SLRHC. This has been very helpful for clinical research studies. The program allows for both inpatient and outpatient studies.

The NY NORC has recruited and trained new young investigators in obesity to join the faculty in the last few years. These include Susan Carnell, Ph.D.; Wendy Chung, M.D., Ph.D.; Karen Dorsey, M.D.; Anthony Ferrante, M.D., Ph.D.; Marci Gluck, Ph.D.; Julia Johnson, Ph.D.; Kathleen Keller, Ph.D.; Simon Klebanov, Ph.D.; Judy Korner, M.D., Ph.D.; Christopher Ochner, Ph.D.; Wei Shen, M.D.; Marie-Pierre St. Onge, Ph.D.; Loren Zeltzer, Ph.D.; Kuan Zhang, Ph.D.; and Yiyang Zhang, Ph.D. These young faculty members have added a large measure of energy and productivity to the Center. Three of them have recently moved on to higher-ranking research positions elsewhere, which we encourage as part of career counseling and development.

The NY NORC has encouraged and nurtured young investigators so they could become competitive for transitional K awards from the NIH. In the last few years, Drs. Anne-Marie Brillantes, Wendy Chung, Anthony Ferrante, Julia Johnson, Kathleen Keller, Judy Korner, Marie-Pierre St. Onge, Loren Zeltzer, and Kuan Zhang have obtained such awards. In addition, other young investigators obtained RO1 and RO3 awards: Drs. Wendy Chung, Anthony Ferrante, Marci Gluck, Mary Horlick, Simon Klebanov, Judy Korner, Wei Shen, Marie-Pierre St. Onge, and Yiyang Zhang. Dr. Chris Ochner received a K CTSA award from the Columbia University CTSA. Dr. Karen Dorsey received a K23 award.