The New York Obesity/Nutrition Research Center
Start Date: 1979
Status: Ongoing
Source of NIH Support: NIDDK
Website: cpmcnet.columbia.edu/dept/obese/NYORC

Organization and Goals

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

- Bring and hold together, under the ONRC'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, post-doctoral fellows, medical students, and doctoral students in basic medical sciences and post-doctoral fellows in obesity and related eating disorders research.
- Engage in enrichment activities that will inform and stimulate the scientists attached to the ONRC to greater research productivity in the field of obesity.

The NY ONRC is a combined effort of St. Luke's-Roosevelt Hospital and Columbia University, with Core Laboratories located in the two institutions, and pilot and feasibility studies funded there and elsewhere in the New York area.

The NY ONRC is made up of 11 Cores, of which 8 are funded by the Obesity/CNRU NIDDK Grant, two are funded by the General Clinical Research Centers NIH grant, and one is self-sustaining.

Core Laboratories

Administrative Core at St. Luke's-Roosevelt/Columbia: F. Xavier Pi-Sunyer, M.D., Director
External Advisory Group Members
Claude Bouchard, Ph.D., Pennington Center, Louisiana State University
Moran, Ph.D., Johns Hopkins University
Albert Stunkard, M.D., University of Pennsylvania
Joseph Nadeau, Ph.D., Case-Western Reserve University

Biostatistics Subcore (of Administrative Core): Harry Kissileff, Ph.D., Director

Hormone and Metabolite Core: F. Xavier Pi-Sunyer, M.D., Director
Mass Spectroscopy Subcore: Dwight Matthews, Ph.D., Director

Body Composition and Energy Expenditure Core: Dympna Gallagher, Ph.D., Director
Room Calorimeter Subcore: Carol Boozer, Ph.D., Director

Molecular Genetics/Molecular Biology Core: Rudolph Leibel M.D., Director

Human Ingestive Behavior Core*:* Harry Kissileff, Ph.D., Director

Adipose Tissue Core: Larry Shapiro, Ph.D., Director

Cores not supported under the NIH ONRC Grant:

GCRC In-Patient Core: (at Columbia-Presbyterian Hospital): H. Ginsberg, M.D., Director

GCRC In-Patient Core: (at St. Luke's-Roosevelt Hospital): J. Albu, M.D., Director

Weight Loss Program of the NY ONRC (Ambulatory Program): X. Pi-Sunyer, M.D., Medical Director; Richard Weil, M.S. and Betty Kovacs, M.S., Associate Directors

Pilot and Feasibility Studies

Completed Pilot and Feasibility (P/F) Grants This Year:

Stress, Cortisol, and Food Intake in Obese Binge Eaters. Marci Gluck, Ph.D.

Acute Regulation of 11-Beta Dehydrogenase by Food Intake *In Vivo* in Humans. Colleen Russell, Ph.D.

Evaluation of Changes in Central Dopamine by Electroretinography. Jennifer Nasser, Ph.D.

The Pattern of Daily Physical Activity for Subjects with Metabolic Syndrome. Kuan Zhang, Ph.D.

Analysis of Gene Expression Profile of Preadipocytes. Yi-ying Zhang, Ph.D.

Newly Awarded P/F Grants:

The Role of Hypothalamic Insulin Signaling in Regulating Lipolysis. Christopher Buettner, M.D. This proposal will study in a mouse model whether intrahypothalamic insulin signaling contributes to the effects of systemic hyperinsulinemia on suppression of lipolysis; which intracellular signaling pathways are activated in adipose tissue by central insulin action; and whether the sympathetic and parasympathetic systems are involved.

Synaptic Excitability of Melanin-Concentrating Hormone Neurons in the Lateral Hypothalamus. Jo Yang-Hwan, Ph.D. This project will explore the neural circuitry that is essential for feeding and energy homeostasis. It will test the hypothesis that endogenous activation of cannabinoid receptors influences the synaptic activity of melanin concentrating hormone neurons.

Hypothalamic Feeding Circuits in Mouse Models of Gestational Diabetes. Lori Zeltser, Ph.D. This study will focus on the intrauterine environment and whether is has long term effects on susceptibility to obesity and diabetes. It is hypothesized that permanent changes in neural circuits in response to differing intrauterine milieus will influence disease susceptibility.

Funding Derived from Previous Pilot and Feasibility Studies

Metabolic Response to Weight Loss in Older Obese Women. Dympna Gallagher, D.Sc. Funding: NIH F32, awarded 1/96; NIH R 29, 12/97 – 11/02.

Does Weight Loss Reduce Mortality Rate Among Obese Rats? Joseph R. Vaselli, Ph.D. Funding: NIH RO1 DK 54298-01, 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. Danielle R. Reed, Ph.D. Funding: NIH RO1, 12/99 – 11/02; NIH DK 03509, 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. Yi-ying 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 Glucoticoids 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. American Diabetes Association. Blandine Laferrere, M.D. 1/1/98 – 12/31/01.

Development of a Genetic Resource: The Molecular Genetics of Obesity in Alaska Natives. Bert Boyer, Ph.D. Funding: NIHF33 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; NIHRO1 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, and 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, HL-70298, 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. 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. Eli Lilly, Co., 3/98 – 3/03.

Molecular Mechanisms for Regional Differences in Adipose Tissue Gene Expression: Possible Role for Leptin. Yiying Zhang, Ph.D. Funding: American Diabetes Association, 1/99 – 12/02.

Molecular Mechanisms for Leptin Effects on Insulin Sensitivity of Hepatic Gluconeogenesis. Yiying 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. Funding: Joseph Vaselli. U.S. 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. 6/1/03 – 7/1/05.

Cloning of a Type 2 Diabetes Modifier in Obese Mice. Wendy Chung and Rudolf Leibel. NIDDK. 9/30/03 – 9/27/07.

Evaluation of the Effects of Dietary-derived Steroids on Muscle Growth in Guinea Pigs. Joseph Vaselli. US Drug Enforcement Agency. 3/1/02 – 2/28/05.

Intramuscular Adipose Tissue Assessment by MRI. Dympna Gallagher. NIH Contract. 8/1/01 – 7/31/03.

Metabolic Effects of Differential Organ Growth Rates. Dympna Gallagher. NIH HD042187. 9/1/03 – 8/31/08.

PPAR-gamma Agonists, Weight gain, and Fat Redistribution. Julia Johnson. 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. New Jersey Foundation for Diabetes Research. 2002.

Glucose-induced Genes Regulating Pancreatic Beta Cell Mass. Anne Marie Brillantes. KO8 award. NIDDK 2002 – 2007.

Mechanism of Positive Energy Balance in PROP Non-tasters. Kathleen Keller. KO1 award NIDDK.

Neuroendocrine Regulation of Energy Homeostasis With Diet and Surgically-induced Weight Loss. Judy Korner. RO3 DK067433, 4/01 – 3/06.

Metabolic and Hormonal Effects of Bariatric Surgery. Judy Korner. RO1 DK072011. 9/05 – 8/10.

Cortisol Stress Response and Intake in Binge Eating Disorder. Marci Gluck. RO3 DK 068392. 2005 – 2007.

Effect of Glycemic Index of a Preload on Food Reinforcement in Humans. Jennifer Nasser. International Life Sciences Institute. 2004 – 2005.

Improving the Energy Cost Estimation of Physical Activity. Kuan Zhang. KO25. DK067976. 7/04 – 6/09.

Leptin Production and Action in Adipocytes. Yi-Ying Zhang. RO1 DK 063034. 7/03 – 6/08.

Core Activities

The Core Laboratories have all remained busy throughout the year. This is attested by the large number of publications emanating from the NY ONRC. The Cores have provided help to

individual investigators and groups of collaborating investigators in the pursuit of their research. These Core Labs continue to provide support that allows for greater efficiency of effort and productivity by the member faculty of the NY ONRC.

Changes to the Core Laboratories in 2004-2005:

The **Mass Spectrometry Core** at the University of Vermont was discontinued as part of the NY ONRC during this year. Funding was provided for one-half year to cover the transition. The Mass Spectrometry Core is being continued in the following manner. The GCRC laboratory at Columbia University has obtained the equipment and is processing samples for the doubly labeled water method. The samples are being prepared for processing at the Hormone and Metabolite (H/M) Lab at St. Luke's-Roosevelt Hospital. The palmitic acid and glycerol samples are being done at the GCRC laboratory at the Mayo Clinic. These samples are also undergoing preliminary preparation at the H/M Core Lab at St. Luke's.

The **Adipose Tissue Core Laboratory** was initiated in the second half of the cycle at St. Luke's Hospital. It is under the direction of Drs. Larry Shapiro and Julia Johnson. The technician is Ping Zhou.

Scientific Advances/Accomplishments

The NY ONRC has led to multiple research collaborations that have resulted in scientific advances in obesity. One focus is on the genetics of obesity, with an effort at identifying genes which are responsible for animal and human disease. Another is in the area of body composition, with efforts at improving the methodology for measuring fat, lean body mass, bone, and skeletal mass. The use of imaging through magnetic resonance has been actively pursued. Another is in the area of energy expenditure. There is also a continuing effort at unraveling the role of gut peptides in food intake regulation and beginning 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. A continuing effort into determining the role of various fat depots in insulin resistance and the differential impact of these depots on differing racial groups has also been undertaken. 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 are strong. The use of Core Laboratories for training, consultation, and service is high. Some of the collaborative studies in the past year are described below.

Korean and Caucasian Overweight Premenopausal Women Have Different Relationship of Body Mass Index to Percent Body Fat with Age. In premenopausal women, we compared body composition in a group of Korean and a group of American women. It was found that the BMI to fat relationship differs significantly in the two groups. For a given BMI, Koreans have a greater amount of body fat. Investigators who use BMI as an index of fatness need to be aware of the differences in the relationship of BMI and fatness across racial/ethnic groups.

Body Fat Distribution after Weight Gain in Women with Anorexia Nervosa. We assessed the fat distribution before and shortly after normalization of weight in women with anorexia nervosa (AN). Hormone levels were also evaluated in patients and control subjects. Re-fed weight in AN did not differ with that of controls. Waist to hip, total trunk fat, visceral fat, and intra-muscular adipose tissue were significantly greater in AN. Total subcutaneous fat and skeletal muscles were not different. Serum cortisol remained higher and estradiol lower in AN.

Thus, recovery in AN was associated with continued abnormalities of the distribution of fat and of important hormones. The long-term implications are not known.

Four Commonly Used Dual-Energy X-Ray Absorptiometry Scanners Do Not Identically Classify Subjects for Osteopenia or Osteoporosis by T-Score in Four bone Regions. We compared four commonly used dual-energy X-ray absorptiometry (DEXA) scanners using a group of subjects. We tested four regions of interest. No two scanners classified subjects identically for osteopenia in any of the four regions. This indicates that classification of bone density in individual subjects using T-scores varies with differing scanners, even scanners made by the same manufacturer.

Air Displacement Plethysmography: Validation in Overweight and Obese Subjects. Patients with moderate and severe obesity, because of their physical size, often cannot be evaluated with conventional body composition measurement systems. The BOD POD air displacement plethysmography (ADP) system can accommodate a large body volume. We compared body volume measured by ADP with measurement by underwater weighing (UWW) in 123 subjects. There was a strong correlation between the two (r=0.94), with no significant bias. Thus, body density, an important physical property used in human body composition models, can be accurately measured by ADP in overweight and obese subjects.

Extracellular Water: Greater Expansion with Age in African-Americans. We examined the cross-sectional relationship between extracellular water (ECW) and age in a large (n=1,538) ethnically diverse group. The cross-sectional relationships between ECW, ICW, and ECW/ICW (E/I) and age were developed using multiple regression modeling methods. Body weight, weight squared, height, age, sex, race, and interactions were all significant ECW predictors. The slope of the observed race x age interaction was significantly greater in African Americans (AA) than in Asians, Caucasians, and Hispanics. A relative ECW expansion (i.e., E/I) was present with greater age in most sex-race groups, although the effect was not significantly larger in AA males compared with the other race groups, except Asians. For females, a larger E/I-age effect was found in AA compared with the other groups. The ECW compartment and E/I are thus variably larger, according to race, in healthy older subjects independent of sex, lean soft tissue, and fat mass.

A Placebo-Controlled, Dose-Ranging Study of a Growth Hormone Releasing Factor in HIV-Infected Patients with Abdominal Fat Accumulation. We investigated the effects of TH9507, a novel growth hormone releasing factor, on abdominal fat accumulation and metabolic and safety parameters in HIV-infected patients with central fat accumulation. TH9507 reduced truncal fat, improved lipid profile, and did not increase glucose levels. Longer-term studies are needed to determine effectiveness of this treatment.

Reproducibility of Pediatric Whole Body Bone and Body Composition Measures by Dual-Energy X-Ray Absorptiometry Using the GE Luna Prodigy. The use of DEXA in pediatrics is increasing. It is a safe, reliable, and easily performed, but there is little information on reproducibility. We evaluated the reproducibility of whole body DEXA scans in children. We found in 49 subjects of 5 to 17 years that body composition and bone mass are highly reproducible among pediatric subjects. The results of this study can be used by clinicians and researchers for interpretation of longitudinal observations and for power calculations.

Bioelectrical Impedance Analysis: Population Reference Values for Phase Angle by Age and Sex. Phase angle is an indicator based on reactance and resistance obtained from bioelectrical impedance analysis (BIA). Although its biological meaning is still not clear, phase angle appears to have an important prognostic role. We did an estimate of population averages and SDs of phase angle that can be used as reference values. BIA and other methods used to evaluate body composition, including hydrodensitometry and total body water, were completed in 1,967 healthy adults aged 18 to 94 years. Phase angle was calculated directly from body resistance and reactance, and fat mass (FM) was estimated from the combination of weight, hydrodensitometry, and total body water by using the 3-compartment Siri equation. Phase angle was significantly smaller in women than in men and was lower with greater age. Phase angle increased with an increase in BMI and was significantly inversely associated with percentage fat in men. Phase angle was significantly predicted from sex, age, BMI, and percentage FM in multiple regression models. In conclusion, phase angle differs across categories of sex, age, BMI, and percentage fat. These reference values can serve as a basis for phase angle evaluations in the clinical setting.

Waist Circumference and Abdominal Adipose Tissue Distribution: Influence of Age and Sex. The influence of age and sex on the distribution of abdominal adipose tissue for a given waist circumference (WC) is unclear. We investigated the influence of age and sex on total abdominal adipose tissue (TAAT), visceral adipose tissue (VAT), and abdominal subcutaneous adipose tissue (ASAT) for a given WC. Within each sex, regression lines between WC and TAAT were not significantly different between younger and older groups. Collapsed across age groups, women had more TAAT for a given WC than did men; however, this difference was significantly reduced with increasing WC. Within each sex, regression lines derived for WC and ASAT were not significantly different between younger and older groups. Collapsed across age groups, women had 1.8 kilograms more ASAT for a given WC than did men across the range of WCs. Within each sex, older men and women had a significantly greater increase in VAT for a given WC than did younger men and women. Furthermore, independent of age group, the slopes for WC and VAT were significantly higher in men than in women. Thus, there are significant sex differences in TAAT, VAT, and ASAT for a given WC. Furthermore, the relation between WC and VAT is substantially influenced by age.

Complete Rescue of Obesity/Diabetes and Infertility in *db/db* Mice with Neuron-Specific LEPR-B Transgenes. We have generated mice that carry a neuron-specific leptin receptor transgene whose expression is driven by the rat synapsin I promoter, SYN-LEPR-B, and mice that are hemizygotes for the transgenes SYN-LEPR-B and NSE-LEPR-B. We have observed a degree of correction in *db/db* mice that are hemizygous and homozygous for SYM-LEPR-B similar to that previously reported for the NSE-LEPR-B transgene. We also show complete correction of the obesity and related phenotypes of *db/db* mice that are hemizygous for both NSE-LEPR-B and SYN-LEPR-B transgenes. Body composition, insulin sensitivity, and cold tolerance are completely normalized in *Nse+Syn db/db* mice at 12 weeks of age compared to lean controls. *In situ* hybridization for LEPR-B expression in *Nse+Syn db/db* shows robust expression in the energy homeostasis relevant regions of the hypothalamus. Expression of the neuropeptide genes, agouti related peptide (*Agrp*), neuropeptide Y (*Npy)*, and proopiomelanocortin (*Pomc*) is fully normalized in dual transgenic *db/db* mice. The two transgenes in concert confer normal fertility to male and female *db/db* mice. Male mice with partial peripheral deletion of *Lepr*, induced in the peri-weaning phase, do not show alterations in body composition or mass. In summary, we have shown that brain-specific leptin signaling is sufficient to reverse the obesity/diabetes/infertility of *db/db* mice.

Role of Peripheral Leptin Receptor in Regulating Systemic Energy Balance and Circulating Leptin Levels. While the importance of central leptin action in energy homeostasis has been well established, the physiological role of peripheral leptin action with regard to energy balance is unclear. We have used a tamoxifen inducible Cre-ER^{T2} transgene to create a mouse model with deficiency of peripheral leptin signaling (Cre-Tam mice). By controlling the dose, route and timing of tamoxifen administration, substantial deletion of exon 17 of Lepr, which inactivates LEPR signaling function, was achieved in multiple peripheral tissues. Lepr in the brain remained intact due to poor permeability of the blood brain barrier to tamoxifen. The effects of the deletion on adiposity were small and sexually dimorphic; a slight, but significant increase in adiposity was observed only in the female Cre-Tam mice (25 percent, $p<0.01$). Food intake, core body temperature, and expression levels of hypothalamic NPY and MCH were not different between the Cre-Tam mice and their controls, as were the responses of the mice to high fat feeding and most of the plasma parameters examined. However, both male and female Cre-Tam mice developed a marked hyperleptinemia (5-8 fold elevation, $p<0.001$) that was associated with increased leptin secretion and percentages of bound leptin in the circulation. Unexpectedly, tissue leptin mRNA levels were not elevated, suggesting that leptin may regulate its own protein synthesis. The results demonstrate that although peripheral leptin action plays a minor role in systemic energy balance, peripheral LEPR, independent of central leptin action, plays a major role in regulating leptin protein synthesis and circulating level and bioavailability of leptin.

FoxO1 Mediates AGRP-Dependent Effects of Leptin on Food Intake. Leptin controls food intake through the actions of orexigenic (Agrp) and anorexigenic (Pomc) hypothalamic peptides. The mechanism by which leptin regulates Agrp and Pomc expression is unclear. We have shown that the transcription factors FoxO1 and Stat3 exert opposing actions on Agrp and Pomc transcription by binding to adjacent sites on the Agrp and Pomc promoters. FoxO1 increases Agrp and decreases Pomc expression, while Stat3 decreases Agrp and increases Pomc expression. These actions occur in a leptin-dependent manner. Remarkably, expression of constitutively nuclear FoxO1 via stereotactic delivery of adenoviruses to the arcuate nucleus blunts leptin's effect to suppress Agrp and curtail food intake. We propose that leptin inhibits food intake via Stat3-mediated squelching of FoxO1-dependent Agrp expression.

Resistance to Dietary Induced Obesity in Female C57BL/6J Mice is Associated with an Increase in Serum Adiponectin and Hypothalamic Leptin Receptor Expression. We have previously demonstrated that female mice of the DBA/2J but not C57BL/6J strain become obese, hyperleptinemic, and subfertile in response to a 24 percent fat by weight diet. The hypothalami of the obese female DBA/2J mice revealed increase NPY expression and diminished expression of LEPR-B and GnRH, suggesting that diminished central leptin effect may contribute to their obese, infertile phenotype. To shed further light on these findings, we assessed body mass, hypothalamic neuropeptide expression, serum adipokine concentrations, and fertility in wild-type female C57BL/6J and DBA/2J mice before and after challenging them with an even higher dietary fat content (35 percent by weight), and compared their parameters to those of female C57BL/6J mice possessing the obesogenic mutations ob/ob and A^{y}/a. After 24 weeks of very high fat feeding, rather than exhibiting an obese, leptin-resistant phenotype like their female DBA/2J counterparts, we found that wild-type female C57BL/6J mice still exhibited minimal weight gain, did not develop infertility and manifested increased hypothalamic expression of LEPR-B with unchanged expression of NPY and GnRH. Although both mutant genotypes were associated with obesity and sub-fertility, the female C57BL/6J ob/ob mice demonstrated significantly increased hypothalamic LEPR-B expression while those with the A^{y}/a genotype

showed a significant reduction. Interestingly, when serum adipokines were compared between members of each strain, female C57BL/6J mice were noted to manifest significantly higher and lower levels of tPAI-1 and adiponectin, respectively, than female DBA/2J mice. This suggests that female C57BL/6J mice possess a strain-specific attenuation of the inflammatory process associated with weight gain that may contribute to their relative resistance to the development of obesity-associated infertility.

Tissue Specific Disruption of Leptin Receptor Signaling Leads to Impaired Insulin Secretion and Glucose Intolerance. The hormone leptin plays a crucial role in the normal maintenance of body weight as well as blood glucose levels. Leptin's effect on blood glucose levels can be indirect, via the regulation of food intake and triglyceride stores, or can be more direct through influencing glucose utilization and production. Additionally, several in vitro studies have suggested that leptin may regulate insulin secretion by pancreatic β-cells by distinct pathways from these other mechanisms. To explore more directly the physiological role of leptin on pancreatic β-cell function and overall glucose homeostasis, we generated mice with an attenuation of leptin receptor signaling in pancreatic β-cells by the use of an insulin promoter driven *cre* transgene in mice with a $lepr^{flox}$ allele. The resulting mice had attenuated leptin receptor signaling in pancreatic β-cells as well as partial attenuation in hypothalamic neurons. The mice were obese and hyperinsulinemic, similar to mice with a global loss of leptin or leptin receptor signaling. However, unlike the case with a global loss of leptin signaling, tissue specific attenuation of leptin receptor signaling resulted in mild-hypoglycemia in the fasting state. In addition, the mice were glucose intolerant and the pancreatic β-cells were defective in glucose stimulated insulin secretion. Collectively, these results highlight a critical role of leptin in modulating pancreatic β-cell function and the involvement of this interaction in type 2 diabetes.

Intramyocellular Lipids (IMCL) in Obese Patients With and Without Type 2 Diabetes: Effects of Weight Loss. It has been proposed that increased IMCL is an independent predictor of insulin resistance. There are conflicting reports regarding differences in the IMCL of obese patients with and without type 2 diabetes and regarding the effect of weight loss on IMCL content in skeletal muscle of patients with type 2 diabetes. We measured IMCL, as the ratio of IMCL to internal water by ^{1}H Magnetic Resonance Spectroscopy (^{1}H MRS) in the tibialis anterior muscle of obese, with type 2 diabetes (n=6, mean ± SEM, age=59±2, BMI=36±1), obese, without type 2 diabetes (n=7, age=56±2, BMI=34±1) and lean healthy controls (n=5, age=33±3, BMI=22±1). All subjects had single voxel ^{1}H MRS performed in the post absorptive phase with controlled physical activity for at least 24 hours prior to the scan. The lean controls (0.018±0.01) had significantly lower IMCL compared to the obese with (0.052±0.009, P=0.03) or without type 2 diabetes (0.047±0.009, P=0.04). There were no differences in the IMCL between the 2 obese groups (P=0.7). The patients with type 2 diabetes (n=5) (participants in Look AHEAD a randomized controlled trial of a lifestyle intervention for weight loss in overweight or obese adults (aged 45-75) with type 2 diabetes) were re-studied after one year in the weight loss intervention. Weight loss ranged from 0 to 14 kg for the 5 type 2 diabetics. While the difference in the mean IMCL before and after weight loss was not significant (0.046±0.009 versus 0.041±0.005, P=0.6), the reduction in IMCL was correlated with the amount of weight loss in the individuals with type 2 diabetes mellitus who lost weight (Spearman correlation=0.90, P=0.037). Thus, in this small sample we did not find a difference in IMCL in obese patients based upon the presence or absence of type 2 diabetes. The patients with type 2 diabetes significantly lowered their IMCL content in proportion to the amount of weight loss. Further studies relating change in IMCL to change in insulin sensitivity during weight loss are ongoing.

Inter-Muscular Adipose Tissue (IMAT) is Increased in Obese Women with HIV Compared to HIV- Controls. Obesity and insulin resistance (IR) are growing problems in HIV+ patients on highly active antiretroviral therapy HAART. We have recently identified IMAT as a depot independently related to IR in HIV– women. This depot has not been studied in HIV+ women. We measured IMAT, subcutaneous adipose tissue (SAT), VAT, and skeletal muscle (SM) volumes by whole body MRI in non-diabetic, obese HIV+ women (mean ± SD)(n=17, age=39±8 BMI=35±3 kg/m^2) and healthy HIV– controls (n=38, age=36±6, BMI=34±6 kg/m^2). Both VAT and IMAT were greater in the HIV+ compared to the HIV– group, after adjusting for age, weight, and height (P<0.05), as well as after adjusting for TAT and/or SM. Total SAT was not different between the groups after adjusting for age, height, and weight, but was lower after adjusting for TAT (P<0.05). The relationship between total SAT and SM was significantly different between groups, with less SAT per SM in HIV+ compared to HIV- (P< 0.05). The absolute values for upper and lower body SAT were not significantly different between groups whereas their relationships with TAT were different, showing a significant upper body distribution of SAT in the HIV+ compared to the HIV–. In conclusion, in obese HIV+ women, adipose tissue is characterized by relatively lower amounts of SAT, with a significant upper body distribution, as well as by higher amounts of both VAT and IMAT. All of these components of adipose tissue distribution could be potentially targeted in intervention studies aimed at reducing IR in obese HIV.

Upper Body Subcutaneous Adipose Tissue Distribution and Increased Inter-Muscular Adipose (IMAT) Tissue Independently Predict Insulin Resistance (IR) in HIV-infected Obese Women. Obesity, upper body adipose tissue (AT) distribution and insulin (IR) are growing problems in HIV+ patients on highly active antiretroviral therapy (HAART). Careful delineation of which aspect of AT distribution predicts IR is important for interventional studies. We found that IMAT was independently related to IR in HIV– women; this has not been studied in HIV+ women. We measured, by whole body MRI, IMAT, VAT, and SAT and their distribution (Leg SAT expressed as percent of total adipose tissue, percent LegSAT) and evaluated their relationships with insulin sensitivity measured by frequently-sampled IVGTT (S_I) in 3 non-diabetic groups a) obese HIV+ women (mean ± SD)(n=17, age=39±8 BMI=35±3); b) HIV- lean and obese controls (C1), n=18 age=34±7, BMI=33±9); and c) obese HIV- matched (by age) controls (C2), n=20, age=37±6, BMI=34±3). The HIV+ women had relatively higher VAT, IMAT, and upper body SAT distribution compared to the combined HIV– controls.

In multiple regression analyses, after controlling for age, weight, and height, both decreased percent LegSAT and increased IMAT were independent predictors of a low S_I in HIV+ (P<0.05 and P=0.05) and IMAT was an independent predictor of S_I in C2 (P<0.05). When groups were combined in a general linear model, no interactions were found between the 3 groups for the regression equations predicting S_I from age, weight, height, skeletal muscle, and percent LegSAT, or IMAT. Both decreased percent LegSAT and increased IMAT independently predicted a low S_I in the combined analysis (P<0.05). VAT was not an independent predictor in any of the groups or in the combined analysis. In conclusion, both SAT distribution and IMAT are independent predictors of IR in obese HIV+ women. Both SAT and IMAT components of AT distribution should be targeted in intervention studies aimed at reducing IR in obese HIV+ women.

Skeletal Muscle, Heparin-Releasable, Lipoprotein Lipase Activity (SM-LPL) Is Increased in Obese African American (AA) versus Caucasian (C) Women, During an Eucaloric Low Fat Diet. We have previously reported lower post-absorptive fat oxidation rates in obese AA compared to C women during an eucaloric 50 percent Fat/ 30 percent CHO diet; however no racial differences were observed in fat oxidation rates during an eucaloric 30 percent Fat/ 50 percent CHO diet. SM-LPL has previously been related to fat oxidation rates in obese individuals. In a prior study, we found no differences in SM-LPL in obese AA versus C women; however, we did not control for diet and physical activity. Therefore, we examined SM-LPL in healthy, pre-menopausal, non-diabetic, obese AA (n=11) and C women (n=6) after an 8-day, eucaloric 30 percent Fat/ 50 percent CHO diet, with controlled diet and physical activity in the GCRC and metabolic chamber. Subjects were age, BMI, and fat matched. Muscle samples were collected through a percutaneous biopsy of the vastus lateralis in the post-absorptive state. We found that the obese AA had significantly greater SM-LPL (0.71 ± 0.12) versus C (0.22 ± 0.16 μmol FFA/g*hour) (P=0.04). On this 30 percent Fat/ 50 percent CHO diet the insulin levels at the time of the biopsy were not significantly different in AA versus C (24.2 ± 9.9 versus 19.8 ± 7.1 μU/ml, P = 0.4) nor were the rates of post-absorptive fat oxidation (176.5 ± 105.8 versus 207.1 ± 96.8 μmol/min, P=0.6). In AA, the elevated SM-LPL suggests increased fatty acid availability for muscle, which would imply a greater utilization. In fact, this is not seen since fat oxidation rates are similar between AA and C. This further suggests a defect in fatty acid utilization independent of SM-LPL. These findings may explain the reported increased fat deposition in skeletal muscle and greater insulin resistance in the AA women.

Antiretroviral Therapy (ART) but not HIV Infection is Associated with Fat Distribution and Increased Subcutaneous Adipose Tissue (SAT) Secretion of IL-6 and TNFα. The relative contribution of HIV infection versus the different components of ART to the pathogenesis of the HIV-associated lipodystrophy syndrome (HIV-L) is not known. The purpose of this study was to compare fat redistribution and adipose tissue (AT) secretion of proinflammatory cytokines in HIV+ on ART, HIV+ naïve to ART, and healthy control subjects. We measured fat distribution and secretion of TNFα and IL-6, in vitro, from abdominal SAT obtained by biopsy from 4 groups of subjects: 29 HIV+ on ART (+) with protease inhibitors (PI+); 22 HIV+ on ART (+) without PI (PI-); 18 HIV+, ART- (naïve); and 14 healthy subjects (control). Whole body SAT and VAT volumes were calculated from MRI and fat distribution (amount of fat in the legs as a percent of total body fat, Leg fat percent) was calculated from DEXA measurements. TNFα and IL-6 secretion were measured during a 3 hour incubation of fat obtained from biopsies of abdominal SAT. SAT amount and Leg fat percent were lower, while secretion of TNFα and IL-6 from SAT were higher, in HIV+ and ART+ patients compared to HIV- controls. In contrast, Leg fat percent as well as proinflammatory cytokines from SAT were not different in HIV+, ART- (naïve) compared to HIV- controls. There was a reduction in the absolute amount of SAT in the HIV +, ART– (naïve) group compared to the controls but this difference was not statistically significant.

These results suggest that increased proinflammatory cytokine production in SAT and fat distribution in HIV+ are specifically associated with ART and not with the HIV infection per se. ART combination in general (drug or immune reconstitution effects) and not PI treatment specifically is likely responsible for SAT inflammation and fat redistribution in HIV-L.

Increased Acute Insulin Response to Glucose (AIR_g) in African American (AA) Women is Independent of Degree of Insulin Resistance (IR) or Glucose Tolerance. AA children are reported to be more insulin resistant than C counterparts. They also have very high AIR_g,

independent of differences in IR. It is not known whether this is also: a) consistently seen in adult AA women; b) true for AA adults with impaired glucose tolerance (IGT) and c) true for IV as well as oral glucose administration. We measured insulin sensitivity (SI), acute insulin response during the first 8 minutes of an IVGTT glucose levels after 75 g oral glucose in AA and C women with normal glucose tolerance (NGT) or IGT. The women were not taking any medications (including oral contraceptives) and had regular menstrual cycles. The IGT women were older and more obese than the NGT women, but in each group the AA and C were matched by age and BMI: NGT AA (n= 52, mean ± SD, age=35±7, BMI=30±6,) and C (n= 43, age = 34±6, BMI = 30±7) and IGT AA (n= 6, age 38±5, BMI = 35±5) and C (n= 6, age 37±7, BMI 37±6).

IGT women had lower SI, lower AIR_g and higher 2 h glucose than NGT women, in both races. Both NGT and IGT AA women had 50 percent higher AIR_g than respective C. They also had different pattern of glucose rise after oral glucose with significantly lower values at 30 minutes, suggestive of increased AIR to oral glucose as well. These differences were independent of differences in weight, fat distribution, or degree of IR. The significance of these findings with regard to progression to diabetes in AA populations needs to be determined.

Choice of Protease Inhibitor (PI) or Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)-Based Highly Active Antiretroviral Therapy (HAART) in HIV-Positive Subjects Affects Postprandial Adiponectin, Free Fatty Acid, Leptin and Insulin Response.
Adipokines leptin and adiponectin as well as insulin resistance are associated with coronary artery disease. There is limited information about the relationships between adipokines, free fatty acids (FFA), and insulin in the postprandial state. We investigated this relationship in a HAART-treated HIV+ population. As PIs in contrast to NNRTIs have been associated with dyslipidemia and insulin resistance, we recruited patients undergoing either PI- and NNRTI-based HAART. Baseline and postprandial insulin, free fatty acids, adiponectin, leptin, lipids, and glucose were measured hourly over a 13 hour period (8 a.m. to 8 p.m.) in 25 non-Caucasian patients (13 women, 12 men) stably treated with HAART >6 months with no signs of treatment failure. Patients were given a standardized AHA Step I diet for breakfast, lunch, and dinner. Comparisons were made between groups treated with PI versus NNRTI (n=13, BMI = 29.75.9 for PI, n=12, BMI = 25.82.8 for NNRTI) and between groups with high (HighIns) and low fasting insulin (LowIns) values split by the median value (22.6 and 11.8 mU/mL for PI and NNRTI, respectively). Day-long glucose levels were not different but day-long insulin levels tended to be higher for PI versus NNRTI (61.7 versus 37.7 mU/mL, p=0.07). FFA levels were suppressed post-prandially in all groups, but to a lesser degree in the PI versus the NNRTI (0.410.03 versus 0.240.03, p<0.0001) and in the HighIns versus LowIns (0.380.03 versus 0.260.03, p<0.0001). Day-long leptin was higher and adiponectin was lower in the PI versus NNRTI (p<0.0001 for both) and in the HighIns versus LowIns groups (p<0.0001 for both). For all subjects, the differences in insulin and FFA levels before and after the breakfast meal were significantly correlated (r=0.4, p=0.049). Postprandial FFA suppression occurs among HIV subjects, regardless of treatment, suggesting responsiveness to physiologic insulin stimulation through food; however, compared to NNRTI-treated subjects, a higher degree of resistance to the anti-lipolytic effect of insulin in the postprandial state was found among PI-treated patients. Leptin and adiponectin levels differed between PI and NNRTI groups, and these adipokines remained essentially stable throughout the day-long period.

Independent Association of Insulin Resistance with Increased Inter-Muscular Adipose Tissue and Larger Acute Insulin Response to Glucose in African American versus Caucasian Non-Diabetic Women. African Americans have higher prevalence of obesity and type 2 diabetes compared to Caucasians. Higher insulin resistance and hyperinsulinemia have been reported in African Americans versus Caucasian adults. Differences in adipose tissue and its distribution may account for these findings. To determine, using whole body magnetic resonance imaging (MRI), in African American versus Caucasian pre-menopausal, non-diabetic women, whether differences in AT and skeletal muscle (SM) volumes account for ethnic differences in insulin resistance measured by intravenous glucose tolerance test (IVGTT). African Americans (n= 32) were 29-42 percent more insulin resistant than Caucasians (n= 28), after adjusting for weight and height or any AT volumes (P<0.05). After adjusting for SM volume the difference decreased to 19 percent and became non-significant. African Americans had a 62 percent larger acute insulin response to glucose (AIR_g); this difference was significant even after adjusting for S_I, weight and height and any MRI measures. Among regional AT volumes, an association independent of race, weight, height, and SM volume was found only between increased IMAT and lower S_I. African American pre-menopausal women had higher insulin resistance and AIR_g compared to Caucasian counterparts. While the difference in insulin resistance was partially accounted for by greater SM volume in the African Americans, the difference in AIR_g was independent of any AT and SM measures and disproportionately larger than expected by the difference in insulin resistance. In addition, whole body IMAT was an important independent correlate of insulin resistance.

Independent Association of Insulin Resistance with Increased Inter-Muscular Adipose Tissue in African American versus Caucasian Non-Diabetic Women. Whole body IMAT, adipose tissue located beneath the *fascia lata* and adjacent to the muscle, measured by whole body magnetic resonance imaging (MRI), is similar in quantity with the visceral adipose tissue (VAT) depot and varies by race. Two previous studies have shown correlations between thigh and whole body IMAT to insulin resistance (IR) but neither showed a relationship independent of body weight, nor did they report on the ethnicity of the populations studied. Independent associations of IR and IMAT may have important implications for the African American populations as African Americans have a higher prevalence of obesity and type 2 diabetes. We measured adipose tissue (AT) depots (VAT, SAT, and IMAT) and skeletal muscle (SM) volumes by whole body MRI and insulin sensitivity (SI) by intravenous glucose tolerance test (IVGTT) in lean and obese African American (n=32, mean ± SD, BMI = 31.5 ± 7.3 kg/m^2) and Caucasian (n=28, BMI = 28.5 ± 6.8 kg/m^2) non-diabetic women. The African Americans were 45 percent more insulin resistant than the Caucasian women (P<0.01). The difference was smaller (28 percent) but still significant after adjusting for weight and height or any AT volume, including IMAT (P<0.05). However, among regional AT volumes, an association independent of race, weight, height, and SM volume was found only between increased IMAT and lower SI (β = -0.35, P=0.028). In conclusion, whole body IMAT is an important independent correlate of IR in pre-menopausal women but differences in IMAT do not entirely explain the higher IR in the African Americans.

Adiponectin Levels During Low and High Fat Eucaloric Diets in Lean and Obese Women. Adiponectin influences insulin sensitivity and fat oxidation. Little is known about changes in adiponectin with changes in the fat content of eucaloric diets. We hypothesized that dietary fat content may influence adiponectin according to an individual's insulin sensitivity. We measured changes in adiponectin, insulin, glucose, and leptin in response to high and low fat eucaloric diets (HF and LF, respectively) in lean (n=10) and obese (n=11) subjects. Obese subjects were

further subdivided in relation to a *priori* insulin sensitivity. We found significantly higher insulin, glucose, and leptin, and lower adiponectin in obese versus lean subjects during both HF and LF. The mean group values of these measurements, including adiponectin (mean ± SD lean - HF 21.9 ± 9.8, LF 20.8 ± 6.6, obese – HF 10.0 ± 3.3, LF 9.5 ± 2.3 ng/ml) did not significantly change between HF and LF diet. However, within the obese group, the insulin sensitive had significantly higher adiponectin during HF than did the insulin resistant subjects. Additionally, the change in adiponectin from LF to HF diet (HF-LF) correlated positively with the obese subjects' baseline insulin sensitivity. Although, in lean and obese women, group mean values for adiponectin did not change significantly with a change in fat content of a eucaloric diet, a priori measured insulin sensitivity in obese subjects predicted an increase in adiponectin during the high fat diet; this may be a mechanism that preserves insulin sensitivity in an already obese group.

Assessment of Human Locomotion by Using an Insole Measurement System and Artificial Neural Networks. A new method for measuring and characterizing free-living human locomotion is presented. A portable device was developed to objectively record and measure foot-ground contact information in every step for up to 24 hours. An artificial neural network was developed to identify the type and intensity of locomotion. Forty subjects participated in the study. The subjects performed level walking, running, ascending and descending stairs at slow, normal, and fast speeds determined by each subject respectively. The device correctly identified walking, running, ascending and descending stairs (accuracy 98.78 percent, 98.33 percent, 97.33 percent, and 97.29 percent respectively) among different types of activities. It was also able to determine the speed of walking and running. The correlation between actual speed and estimated speed is 0.98, $p < 0.0001$. The average error of walking and running speed estimation is -0.050 ± 0.747 km/h (mean ± standard deviation). The study has shown the measurement of duration, frequency, type, and intensity of locomotion highly accurate using the new device and an artificial neural network. It provides an alternative tool to use of a gait lab to quantitatively study locomotion with high accuracy via a small, light, and portable device and to do so under free-living conditions for the clinical applications.

Energy Balance in Early-stage Huntington Disease. Huntington disease (HD) is a genetic neurologic disorder. Weight loss is common in HD and is related to progression of the disease, but the cause of weight loss remains unclear. The study objective was to compare 24 hour energy expenditure (EE) and energy intake in persons with early midstage HD with those of matched control subjects to determine how HD affects energy balance. EE was assessed in 13 subjects with early-stage HD and in 9 control subjects via indirect calorimetry in a human respiratory chamber. Energy intake was determined by weighing all food provided and all leftovers from an ad libitum diet. Body composition was measured via air-displacement plethysmography. Stage of disease was estimated on the basis of the Unified Huntington's Disease Rating Scale and modified Mini-Mental Status examinations. Regression analysis included all 13 HD subjects; *t* tests were used for the comparisons between matched HD and control subjects. The 24 hour EE was 11 percent higher in the HD subjects than in the control subjects (NS). This difference was due to a higher (P =0.043) waking metabolic rate, which was related to a significantly greater displacement of the center of mass by HD subjects than by control subjects (P = 0.028). On average, both groups were in positive energy balance and exceeded their energy expenditure by 2510–2929 kJ.

Higher 24 hour EE in persons with early midstage HD is due to increased physical activity, both voluntary and involuntary. However, HD subjects are able to maintain positive energy balance when offered adequate amounts of food in a controlled setting.

Central Melanocortin Receptor Agonist Reduces Spontaneous and Scheduled Meal Size but Does Not Augment Duodenal Preload-Induced Feeding Inhibition. Central melanocortin (MC) receptor agonists inhibit food intake and may be downstream mediators of the effects of central leptin, which reduces food intake by selectively decreasing meal size and augments the feeding-inhibitory effects of gastrointestinal food stimuli. Central administration of the MC-3/4 receptor (MC-3/4R) agonist, MTII, inhibits feeding in rats, but its effects on meal pattern and potential interactions with gastrointestinal controls of food intake remain unclear. We examined meal patterns and intake in male Sprague-Dawley rats following central intracerebroventricular administration of MTII (0.01-1.0 nmol) in two situations: (1) during daytime 60 minute scheduled access to liquid glucose (12.5 percent) in combination with a duodenal preload of 12.5 percent glucose or physiological saline (4.4 ml/10 min) and (2) during subsequent overnight access to 45 mg of solid chow pellets. Both duodenal glucose preloads and MTII reduced subsequent glucose intake. However, no dose of MTII augmented the reductions in food intake produced by duodenal glucose alone. During overnight access to pelleted chow, the 0.1- and 1.0-nmol doses of MTII reduced food intake, meal size, meal duration, and body weight, and increased the satiety ratio (duration of intermeal interval/preceding meal size) but did not change meal frequency. The present data demonstrate that MTII, like leptin, reduces food intake by a selective reduction in meal size and not meal frequency and suggest that MTII increases the feeding-inhibitory potency of negative feedback signals critical to the control of meal size during spontaneous chow access, but not scheduled access to palatable liquid nutrient solutions.

Effects of Fasting, Leptin, and Insulin on AGRP and POMC Peptide Release in the Hypothalamus. Agouti-related protein (AGRP) and proopiomelanocortin (POMC) have opposing effects on melanocortin receptor (MC-R) signaling and energy balance and are important targets for leptin and insulin in the hypothalamus. While food intake and leptin have documented effects on POMC and AGRP gene expression, and insulin has effects on POMC gene expression, little is known about their effects on POMC or AGRP peptide release. Here we have examined the effects of fasting, leptin, and insulin on the release of AGRP and the POMC-derived peptide gamma(3)-MSH from the perifused rat hypothalamus in vitro. Fasting (48 hours) resulted in a significant overall decrease in gamma(3)-MSH release measured every 20 minutes during a 3 hour baseline perifusion period and after depolarization with 56 mM KCl ($p = 0.02$); there was a trend towards an overall increase in the release of AGRP, but this was not significant. When the ratio of gamma(3)-MSH/AGRP release was calculated at each time point, there was an overall decrease in gamma(3)-MSH/AGRP with fasting ($p < 0.01$). Further examination of the ratio of gamma(3)-MSH/AGRP revealed a 34 percent reduction ($p < 0.05$) in the basal area under the curve (AUC) and a 33 percent reduction ($p < 0.01$) in the post-KCl stimulated AUC in fasted versus fed animals. Also, perifusion of hypothalamic slices with 10(-8) or 10(-7) M leptin for 2 hours resulted in a significant decrease in the release of AGRP noted primarily after depolarization with KCl ($p < 0.01$); no effect was seen on gamma(3)-MSH release. Similarly, in a third experiment, perifusion with 10(-7) M insulin caused a significant decrease in AGRP release ($p < 0.001$) without affecting gamma(3)-MSH release. Thus, there is a significant decrease in gamma(3)-MSH and the ratio of gamma(3)-MSH to AGRP released during fasting, consistent with a net inhibition of hypothalamic MC-R signaling. In contrast, short-term treatment with leptin and insulin may inhibit MC-R signaling primarily by decreasing the release of AGRP.

Transgenic Complementation of Leptin Receptor Deficiency. II. Increased Leptin Receptor Transgene Dose Effects on Obesity/Diabetes and Fertility/Lactation in lepr-db/db Mice. We have generated mice that are homozygous for a leptin receptor transgene that is expressed exclusively in neurons (NSE-LEPR-B). We had previously shown that this transgene in the hemizygous state is effective in ameliorating almost all aspects of leptin receptor deficiency. Now, we show that the transgene, in the homozygous state, almost fully corrects the excess adiposity of LEPR-deficient (db/db) mice. Body composition analyses indicate that the transgene is able to restrain the massive increase in adiposity observed in LEPR-deficient mice. An examination of hypothalamic agouti gene-related peptide and proopiomelanocortin mRNA shows normalization of these leptin-regulated transcripts. Interestingly, despite normalization of circulating leptin concentrations by the transgene in the fed state, transgenic db3J/db mice did not show fasting-induced reductions of circulating leptin. Increased adiposity of the transgenic db/db mice at 4 weeks of age, immediately postweaning, suggests that the transgene is less effective in correcting the preferential fat deposition caused by LEPR deficiency. We noted that the morphology of brown adipose tissue is nearly normal, concordant with the cold tolerance conferred by the transgene. Aspects of the diabetes phenotype are also corrected: glucose and insulin concentrations are nearly normal, and islet hyperplasia is greatly diminished. The transgene also corrects the infertility of db/db females and confers the ability to lactate sufficiently to nurse normal-sized litters. Finally, the slightly increased adiposity and mild insulin resistance of transgenic db/db dams were not a contributory factor to the increased fat content of transgenic db/db male progeny.

A Multi-Center Comparison of Dual Energy X-ray Absorptiometers: *In Vivo* and *In Vitro* Soft Tissue Measurement. To assess intra- and inter-site soft tissue variability by dual energy X-ray absorptiometry (DEXA), we conducted a cross-sectional trial in three medical research institutions. We measured five humans (*in vivo*) and four phantoms (*in vitro*), configured from two whole body phantoms with artificial skeletons and thickness overlays. Doing duplicate total-body DEXA scans on all subjects at each institution within a 15 day period. All intra-site coefficients of variation (CV) were < 0.5 percent for total tissue mass, but in vitro and *in vivo* CVs were 7.2 percent and 2.3 percent for fat mass (FM) and 2.5 percent and 0.9 percent for lean mass (LM), respectively. Several total-body and regional FM and LM measurements were significantly different between sites ($P < 0.05$), with percent differences between sites ranging from 2.6-13.3 percent for FM and from 1.6-13.6 percent for LM. Site 2 was consistently lower for FM and Site 3 was consistently lower for LM. These results stress the need for both rigorous and standardized cross-calibration procedures for soft tissue measurement by DEXA.

Familial Aggregation of Energy Intake in Children. Uncompensated overnutrition promotes obesity, but the controls of children's eating behavior are poorly understood. Insights may be achieved by testing whether the eating patterns of children are associated with demographic variables or whether they aggregate among family members. We tested whether children's total energy intake and macronutrient intake and their ability to compensate for earlier energy intake were associated with sociodemographic variables and anthropometric indexes. We also tested whether these behavioral traits aggregate among siblings. Thirty-two sibling pairs aged 3 to 7 years consumed a multi-item lunch preceded by a low-energy (12.55 kJ) or high-energy (627.60 kJ) preload drink. Mixed-models regression tested the associations between children's energy intake, demographic variables, and anthropometric measures. An intraclass correlation coefficient quantified the family correlation of the measures of children's eating. Children consumed significantly more total energy after consuming the low-energy preload (+/- SD:

2237.39 +/- 1176.45 kJ) than after consuming the high-energy preload (1601.18 +/- 930.65 kJ). Compensation ability was unrelated to the children's age, sex, or ethnicity. Total energy and macronutrient intake, but not compensation propensity, were associated among siblings. The familial association of total energy and macronutrient intakes, independent of anthropometric measures, suggests genetic or home environmental influences specific to these behaviors. Short-term energy compensation, although very accurate within this sample, showed no significant familial correlation.

Adipose Tissue in Muscle: a Novel Depot Similar in Size to Visceral Adipose Tissue. The manner in which fat depot volumes and distributions, particularly the AT between the muscles, vary by race is unknown. The objective was to quantify a previously unstudied and novel IMAT depot and SAT, VAT, and total-body skeletal muscle mass in healthy sedentary African American (AA), Asian, and white adults by whole-body MRI. IMAT is the AT between muscles and within the boundary of the muscle fascia. Analyses were conducted on 227 women [AA (n = 79): body mass index (BMI; in kg/m(2)), 29.0 +/- 5.5; age, 45.7 +/- 16.9 y; Asian (n = 38): BMI, 21.7 +/- 2.9; age, 47.2 +/- 19.9 y; whites (n = 110): BMI, 24.9 +/- 5.4; age, 43.7 +/- 16.2 y]) and 111 men [AA (n = 39): BMI, 25.6 +/- 3.2; age, 45.5 +/- 18.8 y; Asian (n = 13): BMI, 24.9 +/- 2.5; age, 45.6 +/- 25.0 y; white (n = 59): BMI, 25.8 +/- 3.8; age 44.5 +/- 16.3 y]. The results showed that IMAT depots were not significantly different in size between race groups at low levels of adiposity; however, with increasing adiposity, AAs had a significantly greater increment in the proportion of total AT (TAT) than did the whites and Asians (58, 46, and 44 g IMAT/kg TAT, respectively; P = 0.001). VAT depots were not significantly different in size at low levels of adiposity but, with increasing adiposity, VAT accumulation was greater than IMAT accumulation in the Asians and whites; no significant differences were observed in AAs. Race differences in AT distribution extend to IMAT, a depot that may influence race-ethnicity differences in dysglycemia.

Gastric Capacity, Test Meal Intake, and Appetitive Hormones in Binge Eating Disorder. Binge eating disorder (BED), characterized by ingestion of very large meals without purging afterwards, is found in a subset of obese individuals. We showed previously that stomach capacity is greater in obese than in lean subjects, and in this study, we investigated capacity in obese individuals with BED. We also determined ad-libitum intake of a test meal until extremely full. Furthermore, we measured various appetitive hormones (insulin, leptin, glucagon, CCK, and ghrelin) and glucose before a fixed meal and for 120 minutes afterwards. An acetaminophen tracer was used to assess gastric emptying rate. We compared three groups of overweight women: 11 BED, 13 BE (subthreshold BED), and 13 non-binge-eating normals. The BED individuals had the largest stomach capacity as assessed by either maximum volume tolerated (P=.05) or by gastric compliance to pressure (P=.02) using an intragastric balloon. Although test meal intake did not differ between groups, it correlated (P=.03) with gastric capacity. The BED group showed a tendency (P=.06) to have greater area under the curve (AUC) and had higher values at 5 and 60 minutes (P<.05) for insulin compared to normals. Moreover, the BED subjects had lower ghrelin baselines premeal and lower AUC for ghrelin, which then declined less postmeal than for the normals (P<.05). None of the other blood values differed, including glucose, leptin, glucagon, and CCK, as well as acetaminophen, reflecting gastric emptying. The lower ghrelin in BED, although contrary to what was expected, is consistent with lower ghrelin in obesity, and suggests down-regulation of ghrelin by overeating. The lack of differences in CCK is consistent with the lack of differences in gastric emptying rate, given that CCK is released when nutrients reach the intestine. The results show that BED subjects have a large

gastric capacity as well as abnormalities in meal-related ghrelin and insulin patterns that may be factors in binge eating.

Plasma Ghrelin Concentrations are Lower in Binge-Eating Disorder. Binge-eating disorder (BED), characterized by binge meals without purging afterward, is found in about 30 percent of obese individuals seeking treatment. The study objective was to ascertain abnormalities in hormones influencing appetite in BED, especially ghrelin, an appetite-stimulating peptide, which was expected to be elevated. Measurements were made of plasma insulin, leptin, glucagon, cholecystokinin, and ghrelin, as well as glucose following an overnight 12 hour fast, prior to and after ingestion (from 0 to 5 minutes) of a nutritionally complete liquid meal (1254 kJ) at 0830 h, at -15, 0, 5, 15, 30, 60, 90, and 120 minutes. Appetite ratings including hunger and fullness were also obtained. An acetaminophen tracer was used to assess gastric emptying rate. Three groups of comparably obese women (BMI = 35.9 +/- 5.5; percent body fat = 44.9 +/- 4.7) participated: 12 nonbinge eating normals (NB), 14 subthreshold BED, and 11 BED. The BED subjects, compared to NB subjects, had lower baseline ghrelin concentrations prior to the meal, a lower area under the curve (AUC), with lower levels at 5, 15, 30, 90, and 120 min, and a smaller decline in ghrelin postmeal (all $P < 0.03$). The other blood values did not differ among groups, and neither did gastric emptying rate nor ratings of fullness. The BED subjects were then randomly assigned to treatment with cognitive behavior therapy and diet (n = 5) or to a wait list control (n = 4). Baseline ghrelin ($P = 0.01$) and AUC increased ($P = 0.02$), across both conditions, in which most subjects (7 of 9) stopped binge eating. The lower fasting and postmeal plasma ghrelin levels in BED are consistent with lower ghrelin levels in obese compared to lean individuals and suggests downregulation by binge eating.

Effects of Obesity on the Relationship of Leptin mRNA Expression and Adipocyte Size in Anatomically Distinct Fat Depots in Mice. In support of leptin's physiological role as humoral signal of fat mass, we have shown that adipocyte volume is a predominant determinant of leptin mRNA levels in anatomically distinct fat depots in lean young mice in the postabsorptive state. We investigated how obesity may affect the relationship between leptin mRNA levels and adipocyte volume in anatomically distinct fat depots in mice with genetic (Lep(ob)/Lep(ob) and A(y)/+), diet-induced, and aging-related obesity. In all of the obese mice examined, tissue leptin mRNA levels relative to the average adipocyte volume were lower in the perigonadal and/or retroperitoneal than in the inguinal fat depots and were lower than those of the lean young mice in the perigonadal fat depot. A close, positive correlation between leptin mRNA level and adipocyte volume was present from small to hypertrophic adipocytes within each perigonadal and inguinal fat pad in the obese mice, but the slopes of the regression lines relating leptin mRNA level to adipocyte volume were significantly lower in the perigonadal than in the inguinal fat pads of the same mice. These results suggest that obesity per se is associated with a decreased leptin gene expression per unit of fat mass in mice and that the positive correlation between leptin mRNA level and adipocyte volume is an intrinsic property of adipocytes that is not disrupted by adipocyte hypertrophy in obese mice.

Sex-Specific Fat Distribution is not Linear across Pubertal Groups in a Multiethnic Study. We investigated sexual dimorphism and race differences in fat distribution (android/gynoid) before and during puberty. Fat distribution was measured by skinfold thickness and DEXA in healthy African American, Asian, and white subjects (n = 920), divided into pre-, early, and late pubertal groups. Gynoid fat masses adjusted for covariates were lower in late pubertal compared with prepubertal boys, but were not consistently greater in late pubertal compared with prepubertal girls. Progression of sex-specific fat distribution with increasing maturation was

present in Asians only. Among African American and white subjects, early pubertal boys had greater gynoid fat mass compared with the prepubertal group, whereas early pubertal girls had less gynoid fat mass compared with the prepubertal group. Sexual dimorphism in fat distribution was present in all pubertal groups, except among whites at early puberty. Among girls, Asians had lower gynoid fat than whites and African Americans in all pubertal groups. Among boys, Asians had less gynoid fat by DEXA in early puberty and late puberty. Comparison among races demonstrated differences in sexual dimorphism and sex-specific fat distribution with progression in pubertal group. However, in all race groups, the fat distribution of late pubertal boys was more "male" or "android" than prepubertal boys, but late pubertal girls did not differ consistently from prepubertal girls. These findings suggested that the greater sexual dimorphism of fat distribution in late puberty compared with prepuberty may be attributable to larger changes in boys with smaller changes in girls.

Prediction Models for Evaluation of Total-Body Bone Mass with Dual-Energy X-ray Absorptiometry Among Children and Adolescents. The performance of DEXA in identifying children with decreased bone mass is increasing, but there is no consensus regarding how to interpret the results. The World Health Organization diagnostic categories for normal, osteopenia, and osteoporosis, based on T scores, are not applicable to children and adolescents who have not yet reached peak bone mass. The pediatric reference standards provided by DEXA manufacturers have been questioned. Bone mineral density determined with DEXA is "areal" density (a 2-dimensional measurement of a 3-dimensional structure), and its misleading nature among growing and maturing children is well recognized. Few published pediatric reference values for bone mineral density measured with DEXA include factors that are known to affect the results besides age and gender. Our objective was to develop an algorithm for the evaluation of bone mass among children that included known determinants of bone mass and of its measurement with DEXA. Height, weight, pubertal status, and total-body bone mineral content, total-body bone area, and total-body bone mineral density measured with DEXA were recorded for an ethnically diverse group of healthy pediatric subjects (n = 1218; age: 6-18 years). Prediction models for bone measurements were developed and validated with healthy pediatric subjects and then applied to children with medical disorders. There was a significant gender effect, as well as an interaction between gender and ethnicity. Separate models were developed for log total-body bone mineral content, log total-body bone area, and 1/total-body bone mineral density for girls and boys. The variability explained for each measurement increased from level 1, including age and ethnicity (76-86 percent), to level 2, including age, ethnicity, height, and weight (84-97 percent), and to level 3, including age, ethnicity, height, weight, and bone area (89-99 percent). Pubertal stage was an additional significant predictor of bone measurements but increased the explained variability by only 0.1 percent with height and weight in the models. The values predicted with each model were not different from measured values for the validation group but were different for patients with medical disorders, with different patterns according to the diagnoses. These models, including known determinants of bone mass and of bone measurements with DEXA, provide an evaluation of pediatric bone mass that proceeds in steps from level 1 to level 3. The outcomes were different for patients at risk for compromised bone mass, compared with healthy children, with specific patterns for each medical disorder. We propose an algorithm for evaluation of bone measurements that follows levels 1 to 3. Our findings suggest that application of this algorithm to well-characterized groups of pediatric patients could identify disease-specific features of DEXA results. We recommend this approach as a basis for consensus regarding the clinical evaluation of pediatric bone mass, and we suggest that it could lead to meaningful classification of pediatric bone disorders, investigation of pathophysiologic processes, and development of appropriate interventions.

Intermuscular Adipose Tissue-Free Skeletal Muscle Mass: Estimation by Dual-Energy X-ray Absorptiometry in Adults. Skeletal muscle (SM) is a large and physiologically important compartment. AT is found interspersed between and within SM groups and is referred to as IMAT. The study objective was to develop prediction models linking appendicular lean soft tissue (ALST) estimates by DEXA with whole body IMAT-free SM quantified by MRI. ALST and total-body IMAT-free SM were evaluated in 270 healthy adults [body mass index (BMI) of <35 kg/m(2)]. The SM prediction models were then validated by the leave-one-out method and by application in a new group of subjects who varied in SM mass [anorexia nervosa (AN), n = 23; recreational athletes, n = 16; patients with acromegaly, n = 7]. ALST alone was highly correlated with whole body IMAT-free SM [model 1: R(2) = 0.96, standard error (SE) = 1.46 kg, P < 0.001]; age (model 2: R(2) = 0.97, SE = 1.38 kg, P < 0.001) and sex and race (model 3: R(2) = 0.97, SE = 1.06 kg, both P < 0.001) added significantly to the prediction models. All three models validated in the athletes and patients with acromegaly but significantly (P < 0.01-0.001) over-predicted SM in the AN group as a whole. However, model 1 was validated in AN patients with BMIs in the model-development group range (n = 11; BMI of >16 kg/m(2)) but not in those with a BMI of <16 kg/m(2) (n = 12). The DEXA-based models are accurate for predicting IMAT-free SM in selected populations and thus provide a new opportunity for quantifying SM in physiological and epidemiological investigations.

Effects of Roux-en-Y Gastric Bypass Surgery on Fasting and Postprandial Concentrations of Plasma Ghrelin, Peptide YY, and Insulin. To help understand the mechanisms by which weight loss is maintained after Roux-en-Y gastric bypass (RYGBP), we measured circulating concentrations of total and bioactive octanoylated ghrelin, peptide YY (PYY), glucose, and insulin in the fasted state and in response to a liquid test meal in three groups of adult women: lean (n = 8); weight-stable 35 +/- 5 months after RYGBP (n = 12; mean body mass index, 33 kg/m(2)); and matched to the surgical group for BMI and age (n = 12). Fasting plasma total ghrelin levels were nearly identical between RYGBP (425 +/- 54 pg/ml) and the matched controls (424 +/- 28 pg/ml) and highest in lean controls (564 +/- 103 pg/ml). The response to the test meal was comparable between lean and RYGBP groups, with 27 percent and 20 percent maximal suppression, respectively, whereas the magnitude of suppression was significantly diminished in the matched controls (17 percent) compared with the lean group. Fasting levels of octanoylated ghrelin were highest in the lean controls, 220 +/- 36 pg/ml versus 143 +/- 27 in the RYGBP group (P = 0.05) and 127 +/- 12 pg/ml in the matched controls (P < 0.05). The magnitude of maximal postmeal suppression of octanoylated ghrelin was more marked than with total ghrelin, but similar among groups, ranging from 44 to 47 percent. In response to the test meal, there was an early exaggerated rise in PYY in the RYGBP group, such that the peak PYY concentration was 163 +/- 24 pg/ml compared with 58 +/- 17 (P < 0.01) and 77 +/- 23 (P < 0.05) in the matched and lean controls, respectively; the area under the curve at 90 minutes was significantly greater compared with both control groups. Leptin and fasting insulin concentrations and homeostasis model of assessment insulin resistance indices were nearly identical between lean and RYGBP subjects and significantly higher in the BMI-matched controls. In summary, the absence of a compensatory increase in ghrelin concentrations that usually occurs with diet-induced weight loss, and the exaggerated postprandial PYY response after RYGBP, may contribute to weight loss and to the ability of an individual to maintain weight loss after this surgical procedure.

Growth Hormone Releasing Peptide-2 (GHRP-2), Like Ghrelin, Increases Food Intake in Healthy Men. GHRP-2 is a synthetic agonist of ghrelin, the newly-discovered gut peptide which binds to the growth hormone (GH) secretagogue receptor. Ghrelin has two major effects, stimulating both GH secretion and appetite/meal initiation. GHRP-2 has been extensively studied for its utility as a growth hormone secretagogue (GHS). Animal studies have shown its effect on food intake. However, whether GHRP-2 can also stimulate appetite in humans when administered acutely is not known. We subcutaneously infused 7 lean, healthy males with GHRP-2 (1 microg/kg/h) or saline for 270 minutes and then measured their intake of an ad libitum, buffet-style meal. Similar to what has been reported for ghrelin administration, our subjects ate 35.9 +/- 10.9 percent more when infused with GHRP-2 versus saline, with every subject increasing their intake even when calculated per kilogram body weight (136.0 +/- 13.0 kJ/kg [32.5 +/- 3.1 kcal/kg] versus 101.3 +/- 10.5 kJ/kg [24.2 +/- 2.5 kcal/kg], p = 0.008). The macronutrient composition of consumed food was not different between conditions. As expected, serum GH levels rose significantly during GHRP-2 infusion (AUC 5550 +/- 1090 microg/L/240 min versus 412 +/- 161 microg/L/240 min, p = 0.003). These data are the first to demonstrate that GHRP-2, like ghrelin, increases food intake, suggesting that GHRP-2 is a valuable tool for investigating ghrelin effects on eating behavior in humans.

Relation Between Whole-Body and Regional Measures of Human Skeletal Muscle. It is unknown whether regional measures of SM in the thigh and abdomen accurately reflect whole-body SM mass. We aimed to determine whether thigh and abdominal SM measures reflect whole-body SM mass and, if so, which region is a stronger marker. Whole-body and regional measures of SM were obtained by MRI in a sample of 387 white men and women. The regional SM measures, whether obtained by using a single image (midthigh or L4-L5 level) or a series of seven consecutive images covering 31 cm (thigh or abdomen), were strongly correlated with whole-body SM ($P < 0.001$). Independent of sex, the thigh SM measures derived from a single image (men: $R(2) = 0.77$, SEE = 6.5 percent; women: $R(2) = 0.79$, SEE = 7.4 percent) or a series of seven consecutive images (men: $R(2) = 0.84$, SEE = 5.4 percent; women: $R(2) = 0.90$, SEE = 5.1 percent) were stronger correlates of whole-body SM with smaller SEE values than were the abdominal SM measures ($P < 0.01$). However, SM in the abdomen was also a strong marker of whole-body SM, whether determined from a single image at the L4-L5 level (men: $R(2) = 0.63$, SEE = 8.2 percent; women: $R(2) = 0.58$, SEE = 10.4 percent) or from a series of images across the abdomen (men: $R(2) = 0.77$, SEE = 6.5 percent; women: $R(2) = 0.70$, SEE = 8.7 percent). Although thigh measures of SM are better predictors of whole-body SM, a single image within the abdomen routinely used to estimate abdominal fat may also be a useful marker of whole-body SM.

Neuronal Deletion of Lepr Elicits Diabesity in Mice without Affecting Cold Tolerance or Fertility. Leptin signaling in the brain regulates energy intake and expenditure. To test the degree of functional neuronal leptin signaling required for the maintenance of body composition, fertility, and cold tolerance, transgenic mice expressing Cre in neurons (CaMKIIalpha-Cre) were crossed to mice carrying a floxed leptin receptor (LEPR) allele to generate mice with neuron-specific deletion of Lepr in approximately 50 percent (C F/F mice) and approximately 75 percent (C Delta17/F mice) of hypothalamic neurons. LEPR-deficient mice (Delta17/Delta17) with heat-shock-Cre-mediated global LEPR deletion served as obese controls. At 16 wk, male C F/F, C Delta17/F, and Delta17/Delta17 mice were 13.2 ($P < 0.05$), 45.0, and 55.9 percent ($P < 0.001$) heavier, respectively, than lean controls, whereas females showed 31.6, 68.8, and 160.7 percent increases in body mass ($P < 0.001$). Significant increases in total fat mass (C F/F: $P < 0.01$; C Delta17/F and Delta17/Delta17: $P < 0.001$ versus sex-matched, lean controls), and serum leptin

concentrations (P < 0.001 versus controls) were present in proportion to Lepr deletion. Male C Delta17/F mice had significant elevations in basal serum insulin concentrations (P < 0.001 versus controls) and were glucose intolerant, as measured by glucose tolerance test (AUC P < 0.01 versus controls). In contrast with previous observations in mice null for LEPR signaling, C F/F and C Delta17/F mice were fertile and cold tolerant. These findings support the hypothesis that body weight, adiposity, serum leptin concentrations, and glucose intolerance are proportional to hypothalamic LEPR deficiency. However, fertility and cold tolerance remain intact unless hypothalamic LEPR deficiency is complete.

Beta-Cell Function and Insulin Sensitivity in Early Adolescence: Association with Body Fatness and Family History of Type 2 Diabetes Mellitus. The prevalence of type 2 diabetes mellitus (T2DM) among adolescents has increased 5- to 10-fold over the past decade. T2DM results from pancreatic beta-cell dysfunction and insulin resistance. Using rapid IV glucose tolerance testing, we examined beta-cell function and insulin resistance in 72 predominantly Latino eighth grade students (41 males and 31 females; mean +/- sem age, 13.6 +/- 0.1 yr). Thirty-six percent of the children had body mass indexes above the 85th percentile for age and gender, and 50 percent had a first- or second-degree relative with T2DM. Overweight children were five times more likely to be in the highest quartile for insulin resistance. Children with a family history of T2DM were five times more likely to be in the lowest quartile for insulin secretory capacity, 4.5 times more likely to be in the lowest quartile for glucose disposal, and three times more likely to be in the lowest quartile for insulin resistance. These findings are consistent with a model for the physiology of T2DM in which a familial beta-cell dysfunction is unmasked by increasing insulin resistance secondary to overweight in this predominantly Latino population.

Sarcopenia and Increased Adipose Tissue Infiltration of Muscle in Elderly African American Women. Aging is associated with metabolic, physiologic, and functional impairments, in part through age-related changes in body composition. During the later adult years, skeletal muscle mass decreases and body fat becomes centralized. The goal of the study was to investigate body composition over time (+/- SD: 2.04 +/- 0.6 y) in healthy, ambulatory, and elderly African American women. The hypothesis that a reduction in total-body SM and increases in VAT, SAT, and IMAT are ongoing in healthy, weight-stable elderly was tested. The study was a longitudinal evaluation of 26 women (age at baseline: 75.5 +/- 5.1 y) with a BMI (in kg/m(2)) of 27.0 +/- 4.0. Body composition was measured by using whole-body MRI for the quantification of SM, total adipose tissue (TAT), VAT, SAT, and IMAT. SM (P < 0.001) and bone (P < 0.05) masses decreased, and regional analyses showed a decrease in DEXA-derived leg SM (P < 0.05). VAT (P = 0.011) and IMAT (P < 0.001) increased. No changes occurred in TAT (P = 0.45), SAT (P = 0.96), physical function, or food intake. These data show an age-related remodeling of body composition with reductions in SM and corresponding increases in VAT and IMAT. Changes in the previously unstudied depot of IMAT may be involved in the deterioration of metabolic values frequently observed during aging.

Pencil-Beam versus Fan-Beam Dual-Energy X-ray Absorptiometry Comparisons Across Four Systems: Body Composition and Bone Mineral. We compared bone mineral density (BMD) and body fat percentage (percent fat) between two pencil-beam (Lunar DPX and DPX-L) and two fan-beam (Lunar Prodigy, Hologic Delphi A) DEXA systems. We examined these values in the total-body, spine, femur, and forearm scans in 78 healthy adults across these four DEXA systems. BMD and fat values were highly correlated among the four instruments. DPX-L gave the lowest mean percent fat and Prodigy gave the highest mean percent fat for both sexes.

The means were system dependent for percent fat estimates across the four DEXA machines. There was a significant difference detected in BMD estimates across manufacturers, with the Delphi A providing systematically lower values than the Lunar systems in the whole body, spine, and femur sites but higher values than the Lunar systems in the forearm. The present study results show that both percent fat and bone mineral estimates between pencil-beam and fan-beam systems are highly correlated, but vary by system. Significant differences exist between the instruments, especially between different manufacturers, and most of the comparisons are sex dependent. We conclude that longitudinal studies should always be evaluated on the same system when possible, and translation models should be used to assess cross-instrument differences.

Human Cortical Specialization for Food: A Functional Magnetic Resonance Imaging Investigation. Although specialized cortical pathways that process specific sensory stimuli and/or execute cognitive functions have been identified, the neuro-specificity for food-related stimuli has not been clearly demonstrated. We employed functional magnetic resonance imaging (fMRI) to compare neural systems associated with the appreciation of foods and nonfoods. Healthy, normal weight, right-handed men and women (n = 12; age 29.8 +/- 1.8 y, BMI 21.8 +/- 0.8 kg/m(2)) were imaged by fMRI while fasting. Real food and nonfood items were presented to subjects both visually and tactilely during scanning. Subjects were instructed to pay attention to the items. A randomized 2 x 2 block design consisted of 4 conditions: visual food, visual nonfood, tactile food, and tactile nonfood. Brain regions that were significantly activated to a greater extent during the presentation of foods compared with nonfood items included the anterior cingulate, superior temporal gyrus, parahippocampal gyrus, hippocampus, and the insula. These findings support the claim that the presence of food (either seen or felt) elicits a unique cortical response that is differentiated from nonfood items. This neural substrate specialized for processing of foods informs models of food-related behavior.

Metabolic Syndrome in Normal-Weight Americans: New Definition of the Metabolically Obese, Normal-Weight Individual. We determined the prevalence rates and likelihood of the metabolic syndrome and its individual components in normal-weight and slightly overweight individuals (BMI 18.5-26.9 kg/m(2)). There were a total of 7,602 adult participants of the Third National Health and Nutrition Examination Survey, a nationally representative cross-sectional survey. Prevalence and odds ratios (ORs) of the metabolic syndrome, defined according to National Cholesterol Education Program Adult Treatment Panel III criteria, were computed according to 2.0- to 2.5-unit increments in BMI. Depending on ethnicity and sex, the prevalence of the metabolic syndrome increased in a graded fashion from 0.9-3.0 percent at BMI 18.5-20.9 kg/m(2) to 9.6-22.5 percent at BMI 25.0-26.9 kg/m(2). Compared with men with BMI 18.5-20.9 kg/m(2), the odds for the metabolic syndrome were 4.13 (95 percent CI 1.57-10.87) for men with BMI 21-22.9 kg/m(2), 5.35 (2.41-11.86) for men with BMI 23-24.9 kg/m(2), and 9.08 (4.23-19.52) for men with BMI 25-26.9 kg/m(2) after controlling for age, ethnicity, education, income, physical activity, smoking status, and alcohol and total fat, saturated fat, carbohydrate, and fiber intakes. The corresponding ORs in women were 4.34 (2.08-9.07), 7.77 (3.95-15.26), and 17.34 (9.29-32.38). Individuals in the upper normal-weight and slightly overweight BMI range have a relatively high prevalence and are at increased risk of having the metabolic syndrome. Therefore, screening in individuals with normal or slightly elevated BMI is important in the prevention of diabetes and cardiovascular disease.

Dual-Energy X-Ray Absorptiometry-Measured Lean Soft Tissue Mass: Differing Relation to Body Cell Mass across the Adult Life Span. Lean soft tissue (LST) measured by dual-energy X-ray absorptiometry (DEXA) is used as a metabolic measure in aging research despite

evidence of extracellular fluid expansion and a corresponding reduction in body cell mass (BCM) in older participants. We investigated the hypothesis that the fraction of LST as BCM is smaller with greater age. Men and women (n = 2043) had DEXA and 40K-counting for body potassium and BCM measured on the same day. Both BCM and LST were lower with greater age, but the relative lowering was larger for BCM. A multiple linear regression model was fitted with BCM/LST as the dependent variable, and age, sex, and interaction terms as independent variables. Men had a mean BCM/LST greater ($p < .001$) than women; quadratic and cubic age terms were also significant or approached significance. Thus, the fraction of LST as BCM is smaller in older adults, a finding that has implications for the interpretation of DEXA results.

Dual-energy X-Ray Absorptiometry-Measured lean Tissue Mass: Differing Relation to Body Cell Mass across the Adult Life Span. DEXA provides a measure of lean soft tissue (LST). LST hydration, often assumed to be constant, is relevant to several aspects of DEXA body composition estimates. The aims of this study were to develop a theoretical model of LST total body water (TBW) content and to examine hydration effects with empirically derived model coefficients and then to experimentally test the model's prediction that, in healthy adults, LST hydration is not constant but varies as a function of extra- and intracellular water distribution (E/I). The initial phase involved TBW/LST model development and application with empirically derived model coefficients. Model predictions were then tested in a cross-sectional study of 215 healthy adults. LST was measured by DEXA, extracellular water (ECW) by NaBr dilution, intracellular water (ICW) by whole body (40)K counting, and TBW by (2)H(2)O dilution. TBW estimates, calculated as ECW + ICW, were highly correlated with ($r = 0.97$, SEE = 2.1 kg, $P < 0.001$) and showed no significant bias compared with TBW measured by (2)H(2)O. Model-predicted TBW/LST was almost identical to experimentally derived values (means +/- SD) in the total group (0.767 versus 0.764 +/- 0.028). LST hydration was significantly correlated with E/I (total group, $r = 0.30$, SEE = 0.027, $P < 0.001$). Although E/I increased with age (men, $r = 0.48$; women, $r = 0.37$; both $P < 0.001$), the association between TBW/LST and age was nonsignificant. Hydration of the DEXA-derived LST compartment is thus not constant but varies predictably with ECW and ICW distribution. This observation has implications for the accuracy of body fat measurements by DEXA and the use of TBW as a means of checking DEXA system calibration.

Intentional Weight Loss Reduces Mortality Rate in a Rodent Model of Dietary Obesity. We used a rodent model of dietary obesity to evaluate effects of caloric restriction-induced weight loss on mortality rate. In a randomized parallel-groups design, 312 outbred Sprague-Dawley rats (one-half males) were assigned at age 10 weeks to one of three diets: low fat (LF; 18.7 percent calories as fat) with caloric intake adjusted to maintain body weight 10 percent below that for ad libitum (AL)-fed rat food, high fat (HF; 45 percent calories as fat) fed at the same level, or HF fed AL. At age 46 weeks, the lightest one-third of the AL group was discarded to ensure a more obese group; the remaining animals were randomly assigned to one of three diets: HF-AL, HF with energy restricted to produce body weights of animals restricted on the HF diet throughout life, or LF with energy restricted to produce the body weights of animals restricted on the LF diet throughout life. Life span, body weight, and leptin levels were measured. Animals restricted throughout life lived the longest ($p < 0.001$). Life span was not different among animals that had been obese and then lost weight and animals that had been nonobese throughout life ($p = 0.18$). Animals that were obese and lost weight lived substantially longer than animals that remained obese throughout life ($p = 0.002$). Diet composition had no effect on life span ($p = 0.52$). Weight loss after the onset of obesity during adulthood leads to a substantial increase in longevity in rats.

Central Infusion of Agouti-Related Peptide Suppresses Pulsatile Luteinizing Hormone Release in the Ovariectomized Rhesus Monkey. Agouti-related peptide (AGRP), an endogenous melanocortin receptor antagonist, is a powerful orexigenic peptide when infused centrally. AGRP and neuropeptide Y (NPY), another orexigenic peptide, are colocated within the same neurons in the arcuate nucleus. Both NPY and AGRP mRNA expression increases during food restriction, a condition that is known to suppress the GnRH pulse generator and reproductive function. Although NPY has been shown previously to suppress LH secretion in the ovariectomized monkey, data on AGRP are lacking. In this study, we examined the effect of AGRP infusion into the third ventricle on pulsatile LH release in five adult monkeys. The 8-h protocol included a 3-h intraventricular saline infusion to establish baseline pulsatile LH release, followed by a 5-h infusion of AGRP (83-132) [5 microg/h (n=1) or 10 microg/h (n=4)]. In separate experiments, each animal received an 8-h saline treatment as a control. Blood samples were collected every 15 minutes for LH measurements. Cortisol levels were measured every 45 minutes. AGRP infusion significantly decreased LH pulse frequency (from a baseline of 0.74 +/- 0.07 pulse/h to 0.36 +/- 0.12 during AGRP infusion; P <0.01) and mean LH concentrations (to 41.1 +/- 7.5 percent of baseline by h 5 of AGRP infusion; P < 0.001). LH pulse amplitude was not modified by AGRP treatment. AGRP infusion also significantly increased cortisol release, as previously reported. The data demonstrate that central administration of AGRP inhibits pulsatile LH release in the monkey and suggest that AGRP, like NPY, may mediate the effect of a negative energy balance on the reproductive system by suppressing the GnRH pulse generator.

Improving Energy Expenditure Estimation for Physical Activity. The purpose of this study was to validate the Intelligent Device for Energy Expenditure and Activity (IDEEA) for estimation of energy expenditure during a variety of activities. An additional aim was to improve the accuracy of the estimation of energy expenditure of physical activity based on second-by-second information of type, onset, and duration of activity. This study included two tests: a mask calorimetry test with 27 subjects [age = 33.7 +/- 13.8 (mean +/- SD) yr; BMI = 24.8 +/- 4.8 kg x m] and a respiratory chamber calorimetry test with 10 subjects (age = 32.9 +/- 12.4 yr; BMI = 26.1 +/- 5.6 kg x m). In the mask test, the subjects performed activities (sitting, standing, lying down, level treadmill walking, and running at different speeds) for 50-min durations. For the chamber test, subjects lived in the metabolic chamber for 23 hours and performed three exercise sessions to compensate for the confined environment. The results showed significant correlations (P < 0.0001) between energy expenditure estimated by IDEEA and energy expenditure measured by the calorimeters with an accuracy >95 percent. After corrections for the decrease in sleeping metabolic rate, the estimation accuracy for the chamber test was increased by 1-96.2 percent, whereas the estimation accuracy for nighttime activity was significantly improved by 4-99 percent. IDEEA provides a suitable method for estimating the energy expenditure of physical activity and provides both instantaneous and cumulative estimates of energy expenditure over a given period.

Lifestyle Behaviors Associated with Lower Risk of Having the Metabolic Syndrome. The metabolic syndrome is a cluster of risk factors that predisposes individuals to cardiovascular disease (CVD) and diabetes and is present in almost one fourth of adult Americans. Risk factors involved with the metabolic syndrome can be altered via modifiable lifestyle factors, such as diet, physical activity, and smoking and drinking habits. The objective of this study was to examine the extent to which these modifiable lifestyle behaviors are associated with the risk of having the metabolic syndrome. Data from the Third National Health and Nutrition Examination Survey (NHANES III), conducted between 1988 and 1994, were used to measure the risk of having the metabolic syndrome in healthy adult Americans who follow certain lifestyle

behaviors, such as dietary practices, levels of physical activity, and smoking and drinking habits. Low physical activity level, high carbohydrate (CHO) intake, and current smoking habits were all significantly associated with an increased risk of having the metabolic syndrome, even after adjusting for other related covariates. Relative to physically inactive subjects, being physically active was associated with lower odds ratio (OR) (0.36, confidence interval [CI] 0.21 to 0.68, P < .01) in overweight men and in normal weight (0.36, CI 0.18 to 0.70, P < .01) and overweight (0.61, CI 0.38 to 0.97, P < .05) women. Although the type of CHO could not be distinguished, relative to a high CHO diet, men having a low or moderate CHO intake had a lower risk of having the metabolic syndrome with respective ORs of 0.41 (CI 0.24 to 0.67, P < .01) and 0.44 (CI 0.25 to 0.77, P < .01); no effect of dietary CHO was observed in women. Moderate alcohol consumption was not significantly related to the risk of having the metabolic syndrome in men, but was associated with a lower OR in women (0.76, CI 0.61 to 0.95, P < .05). Regression models indicate a reduced risk of having the metabolic syndrome when selected low-risk lifestyle factors are present in combination, particularly in subjects with body mass index (BMI) < 30 kg/m(2). According to our cross-sectional logistic models, the risk of having the metabolic syndrome is substantially lower in individuals who are physically active, nonsmoking, have a relatively low CHO intake and moderate alcohol consumption, and who maintain a BMI in the non-obese range. These observations have potentially important value for public health recommendations.

Combination of BMI and Waist Circumference for Identifying Cardiovascular Risk Factors in Whites. BMI (kilograms per meters squared) and waist circumference (WC) (measured in centimeters) are each associated with the risk of developing CVD. Therefore, a combination of the two may be more effective in identifying subjects at risk than either alone. The present study sought to identify the combination of BMI and WC that has the strongest association with CVD risk factors in whites. Subjects were 8,712 white men and women from the Third National Health and Nutrition Examination Survey. The optimal combination of BMI and WC was developed using logistic regression models with BMI and WC as predictors and CVD risk factors as outcomes. The combined measure of BMI and WC using current cut-off points was also examined. Sensitivity, specificity, and receiver operating characteristics curves were compared between the combined measures and BMI alone. For white men, the optimal combination of BMI and WC for identifying CVD risk factors was 0.68 x BMI + 0.32 x WC. This combination generated a score that better estimated the odds of having CVD risk factors than either alone. For white women, WC alone largely determined the likelihood of having CVD risks. The combination of BMI and WC using current cut-off points may provide an improved measure of CVD risk. Combined measures showed a higher sensitivity or a shorter distance in receiver operating characteristic curves in the identification of CVD risk factors. Combined measures of BMI and WC may provide a higher overall test performance for CVD risk factors and may be useful in some ethnic groups as an improved means of screening subjects for further evaluation in the clinical setting.

Personnel Changes

During the past year, Dr. Steven Heymsfield resigned from Columbia University and took a position with industry. Dr. Dympna Gallagher was appointed to replace him as Director of the Body Composition Core Laboratory.

Dr. Mary Horlick resigned from our member faculty to join the National Institutes of Health in Washington.

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 ONRC is a site for both the Diabetes Prevention Trial and the Look AHEAD trial, each of which has a substantial overrepresentation of minority subjects, so that there will be the ability to analyze separately for minority groups. The NY ONRC is pursuing a systematic study of the metabolic differences in black and white women in relation to body fatness and body fat distribution. Differences between black and white women have been found, and are being pursued. The Rosetta study in children is following minority children through the various Tanner stages for a comparative evaluation of body compositional changes in Caucasian, Black, Asian, and Hispanic children. A pilot study has just been completed in a group of minority junior high school children in Manhattan. This pilot has examined the prevalence of pre-diabetic risk factors and the response of the risk factors to an exercise, health, and nutrition education program and evaluated its effectiveness. Its success has prompted us to apply for a more extensive grant to pursue this program.

Obesity. All of our investigation is focused on research on this condition. The research is at the basic, the animal, and the human levels. Because of the expertise of the investigators at the NY ONRC, we do a great many clinical trials of new drugs being developed for weight loss.

AIDS. The NY ONRC is studying the increased central fat distribution that comes with longtime HIV infection or its treatment. The metabolic health risks of this condition are being measured in cross-sectional and longitudinal studies.

Health Promotion and Disease Prevention.
Diabetes Prevention Program (DPP). The existence and available resources of the NY ONRC was helpful in initiating a grant for St. Luke's-Roosevelt Hospital to be one of the Centers in the NIH Diabetes Prevention Program (DPP). The purpose of this program has been 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. Dr. X Pi-Sunyer is the principal investigator, and Ms. Jane Lee is the Coordinator. The study was terminated early by the Data Monitoring Board because both the lifestyle and drug arms significantly decreased conversion to diabetes as compared to the placebo control. The trial is continuing for another 5 years to obtain more secondary end point results.

The Look AHEAD Trial. The existence and available resources of the NY ONRC were helpful in initiating a grant for St. Luke's-Roosevelt Hospital to be one of the Centers in the NIH Look AHEAD Trial. Dr. X. Pi-Sunyer is the principal investigator and Ms. Jennifer Patricio is the Coordinator. Look AHEAD is a multi-center, randomized clinical trial designed to determine whether interventions for producing sustained weight loss in obese individuals with type 2 diabetes will improve over-all 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. The protocol has begun and recruitment has already signed up one half of the required volunteers. Dr. Pi-Sunyer is co-Chair of the study.

Bari 2D Trial. In a similar manner, the existence and resources of the NY ONRC were important in our being a site for the Bari 2D trial. This NIH supported trial is designed to test two hypotheses: (1) coronary revascularization hypothesis: that a strategy of initial elective re-vascularization 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 <7.0 percent, 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 is the principal investigator at this site.

Educational Activities/Accomplishments

Pilot and Feasibility (P/F) Program. The NY ONRC supports a P/F grant research program of up to $25,000 annually to investigators 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 ONRC has two weekly research seminar series (one at each of the sites: St. Luke's and Columbia Medical Center), a monthly appetitive seminar for all, and two mini-symposia per year. A journal club meets weekly. The NY ONRC also has a visiting scientist program. This year there have been visiting scientists from Korea, China, and Germany staying for a minimum of a year.

Post-doctoral Training Program. The NY ONRC has an NIH-sponsored post-doctoral training program in obesity with five slots. The Institute of Human Nutrition at Columbia, of which the ONRC is a part, has both a pre- and a post-doctoral training grant in Nutrition. We have recently received post-doctoral grants of 2 years each from the New York Empire State foundation, given to two of our promising young M.D. investigators.

Professional Education. The NY ONRC is one of the eight sites of CORE, whose mission is to educate physicians and other health professionals in the management of obesity. The NY ONRC provides half-day workshops for both resident and practicing physicians throughout the year. These are held both at the NY ONRC site and at other sites in the New York metropolitan area and even further. Workshops have been held in Washington and in Connecticut, as well as New York and New Jersey. Evaluations of these workshops have been outstanding. With this program, we are reaching over 300 physicians a year. We have recently received an award from the Josiah Macy Foundation to expand this work.

Nutrition Courses. The faculty, as members of the Institute of Human Nutrition at Columbia, participate in a required one-semester course in the first year of medical school. Further, the NY ONRC 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 ONRC welcomes students from nutrition programs at Columbia's Institute of Human Nutrition and Columbia Teachers' College. The NY ONRC provides residents and fellows in medicine teaching and training in clinical and basic nutrition. In addition, the faculty offer research electives in nutrition/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.

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

Website. The NY ONRC has a website (*cpmcnet.columbia.edu/dept/obese/NYORC)* on which information about the Center, its Core Laboratories, and its research activities are posted.

Media. NY ONRC 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 ONRC 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 ONRC

The NY ONRC provides expertise for the treatment and investigation of obesity and eating disorders. The NY ONRC has been instrumental in organizing an active program in obesity surgery. It has also helped to organize a sleep laboratory and an obesity medical treatment center.

The presence of the NY ONRC 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, in ingestive behavior, and in body composition have occurred. The NY ONRC imparts knowledge and biological samples to other investigators both within and outside the Center.

The different but complementary interests of the different cores at the two institutions have put the NY ONRC 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 ONRC to train new scientists for careers in obesity research.

In addition, the NY ONRC investigators use the General Clinical Research Center at Columbia University and the satellite GCRC at St. Luke's Hospital. This has been very helpful for clinical research studies. Until four years ago, the program was only inpatient, but an ambulatory program has now also been funded and is very active.

The NY ONRC has recruited and trained new young investigators in obesity to join the faculty in the last few years. These include Mary Ann Brillantes, M.D., Wendy Chung, M.D., Ph.D., Anthony Ferrante, M.D., Ph.D., Marci Gluck, Ph.D., Mary Horlick, M.D., Julia Johnson, Ph.D., Simon Klebanov, Ph.D., Judy Korner, M.D., Ph.D., Yi-Ying Zhang, Ph.D., Kathleen Keller, Ph.D., and Kuan Zhang, Ph.D. These young faculty members have added a large measure of energy and productivity to the Center.

The NY ONRC has encouraged and nurtured young investigators so that they could become competitive for transitional K awards from the NIH. In the last four years, Drs. Julia Johnson,

Anthony Ferrante, Mary Ann Brillantes, Wendy Chung, Judy Korner, Kathleen Keller, and Kuan Zhang have obtained such awards. In addition, four other young investigators, Drs. Mary Horlick, Simon Klebanov, Marci Gluck and Yi-Ying Zhang obtained RO1 and RO3 awards.