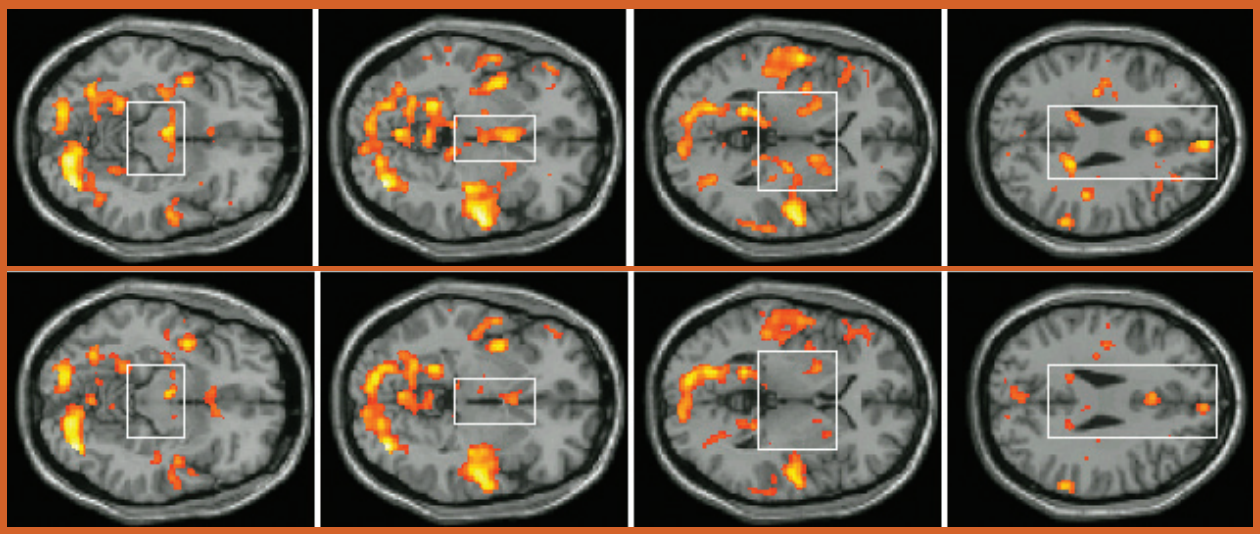


Gastric bypass surgery, a treatment for extreme obesity, is performed on the digestive tract. Its effects, however, also reach to the brain to reduce the appeal of high-calorie food. In a recent study described in this chapter, researchers recruited volunteers who were planning to have gastric bypass surgery, and used functional magnetic resonance imaging to scan their brains before surgery and 1 month after surgery. During the imaging sessions, volunteers were shown pictures of calorie-dense foods (pizza and cake) and low-calorie foods (raw vegetables) to see whether the pictures, along with recordings of the names of the foods, would activate areas of the brain. The researchers found that brain responses to all food, but especially high-calorie foods, were notably diminished after surgery, particularly in areas known to process decisions to pursue rewarding, enjoyable experiences. Images left to right each show a different area of the brain (depicted in gray); images in the top row represent responses to high-calorie foods, whereas those in the bottom row represent responses to lower-calorie foods, with each showing the same area of the brain as the image directly above. The bright orange and yellow colors highlight areas with greater brain activity prior to surgery compared to a month after surgery. That is, if brain activity differed before and after surgery, the area where there was a difference is marked in yellow/orange. Within the boxed areas (comparing each image to the one directly below it), the yellow/orange spots are larger in the top row than in the bottom row, reflecting the fact that the surgery changed brain responses to high-calorie foods more than to lower-calorie foods. When asked how the pictures of foods made them feel, the volunteers reported less inclination to eat after surgery, and they no longer preferred high-calorie foods, consistent with the patterns of activity in the brain images. While gastric bypass surgery is designed to restrict calorie intake by modifying the structure of the digestive tract, these new findings help explain an additional way in which this surgery may lead to substantial weight loss—through loss of preference for high-calorie foods.

Images provided by Dr. Allan Geliebter, and reprinted from Ochner CN, Kwok Y, Conceição E, Pantazatos SP, Puma LM, Carnell S, Teixeira J, Hirsch J, and Geliebter A. Selective reduction in neural responses to high calorie foods following gastric bypass surgery. Annals of Surgery 253(3): 502-507, 2011; permission conveyed through Copyright Clearance Center.

Obesity

Obesity has risen to epidemic levels in the United States. Individuals who are obese may suffer devastating health problems, face reduced life expectancy, and experience stigma and discrimination. Obesity is a strong risk factor for type 2 diabetes, fatty liver disease, and many other diseases and disorders within the NIDDK's mission.

Approximately one-third of U.S. adults are considered obese based on body mass index (BMI), a measure of weight relative to height.[1,2] Nearly 17 percent of children and teens ages 2 through 19 are also obese, and thus at increased risk for developing serious diseases both during their youth and later in adulthood.[3] Obesity disproportionately affects people from certain racial and ethnic groups and those who are socio-economically disadvantaged.

The high prevalence of obesity in the United States is thought to result from the interaction of genetic susceptibility with behaviors and factors in the environment that promote increased caloric intake and sedentary lifestyles. Research is providing the foundation for actions to address this major public health problem by illuminating the causes and consequences of obesity, evaluating potential prevention and treatment strategies, and providing an evidence base to inform policy decisions. The NIDDK supports a multi-dimensional research portfolio on obesity, spanning basic, clinical, and translational research. NIDDK-funded studies for preventing and treating obesity span behavioral and environmental approaches in families, schools, and other community settings; medical interventions; and combinations of these strategies. In parallel, Institute-supported investigations into the biologic processes associated with body weight will spark new ideas for intervention approaches. To help bring research results to health care providers and the public, the Institute also sponsors education and information programs.

The NIDDK also continues to play a leading role in the NIH Obesity Research Task Force. The NIDDK Director co-chairs the Task Force along with the Directors of the National Heart, Lung, and Blood Institute, and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development. The Task Force includes representatives from these and numerous other NIH Institutes, Centers, and Offices. In 2011, the Task Force released an updated *Strategic Plan for NIH Obesity Research*, which was developed with extensive external input from researchers across the country, professional and other health-focused organizations, and others. The new *Strategic Plan* reflects the exciting opportunities that have emerged from research progress in the years since the NIH developed its first strategic plan on this major public health challenge.

Highlights of recent advances from NIDDK-supported research on obesity are provided in this chapter. These represent examples of the NIDDK's broad spectrum of research efforts toward reducing the burden of obesity so that people can look forward to healthier lives.

GENETICS OF BODY WEIGHT AND ASSOCIATED CONDITIONS

Further Unraveling the Genetic Basis of Obesity: Scientists have uncovered 18 new genetic variants that predispose people to increased body mass index (BMI), a commonly used measure of obesity. A variety of factors contribute to risk for obesity: behavior, environment, and biology—including

[1] *Statistics Related to Overweight and Obesity. http://win.niddk.nih.gov/statistics/index.htm*

[2] *Flegal KM, et al. JAMA 303: 235-241, 2010.*

[3] *Ogden CL, et al. JAMA 303: 242-249, 2010. For children and adolescents, obesity refers to a BMI at or greater than the 95th percentile on growth charts (which are based on previous national surveys).*

genetic factors. Over the past few years, several genes have been discovered that influence body weight, but together only account for a fraction of all of the genetic determinants of obesity. To gain further understanding of the genes that regulate body weight, researchers sought to identify new genetic variants that associate with BMI—a calculation of weight relative to height—which is a simple and noninvasive measure of obesity. Scientists used several genome-wide association (GWA) studies to scan 2.8 million individual genetic variants in the DNA of nearly 250,000 people of European ancestry to find variants that associate with BMI. When the researchers analyzed data from GWA studies, they confirmed all 10 genetic variants that had previously been shown to associate with BMI, and also uncovered 22 new variants. Four of these 22 genomic regions were known from prior studies to be associated with obesity-related characteristics, such as body weight or increased waist circumference, narrowing the list to 18 new genetic variants that were not known previously to be associated with obesity. The genomic regions found to be associated with BMI implicate a range of biological processes and pathways in obesity risk, including gene regulation, brain function, and immunity.

Importantly, the researchers found that some BMI-associated genetic variants were also linked to metabolic traits such as insulin resistance, elevated blood lipid levels, and type 2 diabetes. One particularly interesting gene associated with increased BMI, *GIPR*, was also associated with increased glucose uptake by the body after carbohydrate ingestion. This link was surprising because often increased BMI is linked to reduced glucose uptake, indicating insulin resistance. These findings emphasize the complex genetic foundation for obesity, metabolism, and disease, with many genes providing varying degrees of influence. Researchers believe that this newly expanded list of genetic variants associated with BMI still only accounts for a small fraction of the genes that affect obesity. Therefore, additional avenues of research may help attain a more comprehensive understanding of body weight genetics.

Speliotes EK, Willer CJ, Berndt SI, et al. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. Nat Genet 42: 937-948, 2010.

Genetic Variants Help Determine Body Fat Distribution: Scientists have identified 13 new genetic variants associated with waist-hip ratio, several of which appear to exert effects only in women. While obesity can be characterized as a condition of excess body weight, there are many approaches to measuring obesity, including BMI, or weight relative to height; overall body fat percentage; waist circumference; and waist-hip ratio (WHR), which reflects body fat distribution. A larger waist-hip ratio has been associated with serious health conditions such as type 2 diabetes and cardiovascular disease, and these increased health risks may occur even if a person's BMI is within the normal range. Analyses from previous obesity studies have suggested that the genetic factors that influence WHR are largely distinct from those that affect other measures of obesity, such as BMI. Prior studies have also shown that WHR is strongly influenced by genetics, but specific regions of the genome contributing to WHR remain largely undiscovered.

In this study, researchers surveyed the DNA from hundreds of thousands of individuals, using data from many large-scale GWA studies, and examined the links between WHR and each of millions of regions of the genome. Through their extensive analyses, scientists found that 14 genetic variants associated with WHR, although one of these had been previously identified. Of the 14 genetic variants, only four exhibited an association with BMI, suggesting that the genetic factors contributing to these two measures of obesity are largely independent of one another. Seven of these new genetic variants had large effects only in women. The scientists found that the genetic variants were also associated with increased circulating fats, harmful cholesterol, and insulin resistance—all indicators of metabolic disease. Eleven of the genetic variants were also associated with type 2 diabetes.

When examining the functions of genes within these genomic regions, the scientists found that they were involved in a range of biological processes, including fat cell development, regulation of fat molecule production, embryonic development, blood vessel formation, and insulin response. Interestingly, five of the genes identified in this study were turned on differently in fat tissue from the buttocks or the waist, suggesting that the differential action of the genes in

specific regions of the body could be linked to variation in body fat distribution. Together with results from GWA studies investigating other measures of obesity (also described in this chapter), research scientists are gaining a more detailed picture of the genetic foundation of this complex condition.

Heid IM, Jackson AU, Randall JC, et al. Meta-analysis identifies 13 new loci associated with waist-hip ratio and reveals sexual dimorphism in the genetic basis of fat distribution. Nat Genet 42: 949-960, 2010.

Risk Variations Discovered for Nonalcoholic Fatty Liver Disease: Research scientists studying the heritability of nonalcoholic fatty liver disease (NAFLD) have identified genetic variants that increase disease susceptibility. NAFLD ranges in severity from accumulation of fat in the liver, without injury, to the presence of liver fat with varying degrees of inflammation and scarring, which are associated with liver fibrosis and cirrhosis and which can progress to liver failure and the need for liver transplantation. This study looked at the heritability of NAFLD, identified risk variants associated with NAFLD, and defined the metabolic consequences of these variants.

Although evidence indicating that genetic factors contribute to NAFLD existed, heritability for this disease needed to be established and quantified, and few risk variants had been identified thus far. The researchers began this study with data collected by the Genetics of Obesity-related Liver Disease (GOLD) consortium, which consists of cohorts from four existing consortia, three of which include families. The members of the GOLD patient cohort had been diagnosed with NAFLD using imaging by computed tomography (CT), a noninvasive method to quantitatively measure liver fat. Analysis of data from the three family-based GOLD cohorts confirmed that CT-diagnosed NAFLD does, indeed, have a genetic component that is estimated to be between 26 percent and 27 percent. Next, the researchers used data from all four GOLD cohorts to search for NAFLD susceptibility variants. Genome-wide association studies were conducted separately on samples from each cohort. The results of the four studies were combined in a "meta-analysis" that identified three variants significantly associated with NAFLD—including one variant that had been identified previously. Additional analysis uncovered other possible variants. To study these potential variants further, the scientists sought to determine whether any were associated with another measure of NAFLD, based on biopsies collected in the NIDDK's Nonalcoholic Steatohepatitis (NASH) Clinical Research Network. This NASH network consists of patients who have fatty liver disease with fibrosis. Association studies with the NASH cohort and NAFLD variants showed that four of the variants identified in the GOLD cohorts also were associated with this liver disease in the NASH cohort; a fifth was only associated with CT-measured disease. Because earlier epidemiology studies linked NAFLD to metabolic traits, the variants were examined individually for effects related to these traits, including cholesterol, triglycerides, blood sugar, insulin resistance—a risk factor for diabetes, and obesity. The researchers found that three of the variants had effects on specific metabolic traits. The distinctive patterns of these metabolic effects suggest that the variants involve different metabolic pathways.

This study demonstrated that NAFLD is a genetic disease, determined the extent of its heritability, and identified five risk variants. The researchers combined study results with new technologies in inventive ways to determine which genes may be influenced by the variants and to elucidate the distinct patterns of metabolic traits affected. These patterns indicate involvement of different metabolic pathways and suggest that the pathways may provide multiple targets for drug development.

Speliotes EK, Yerges-Armstrong, LM, Wu J, et al. Genome-wide association analysis identifies variants associated with nonalcoholic fatty liver disease that have distinct effects on metabolic traits. PLoS Genet 7: e1001324, 2011.

Gene Variant Links Low Body Fat Percentage to Increased Diabetes Risk in Men: Using DNA from tens of thousands of individuals, researchers have identified genetic variants at two regions of the genome that are associated with reduced body fat percentage, one of which was also linked to increased risk for type 2 diabetes and cardiovascular disease in men. In addition to behaviors like dietary habits and exercise frequency, genetic factors are known contributors to obesity. Recent GWA studies have uncovered many

genes associated with BMI, which has been used as a surrogate for obesity. Since body weight is a sum of both lean and fat mass, genes associated with weight may not reflect an association with excess fat. Scientists had not looked as extensively for genes that specifically affect the amount of body fat.

In this study, scientists took advantage of several large-scale GWA studies, including more than 76,000 individuals, to find genetic variants that are associated with body fat percentage. The researchers looked for variants in approximately 2.5 million regions of the genome, and found 14 that seemed to have some association with body fat percentage. Further analysis narrowed their focus to three of these variants, including one that had previously been identified as associated with obesity and body fat. The other two variants were in genes not previously known to play a role in body fat, and both were associated with reduced body fat percentage. The researchers investigated links between the two newly identified gene variants and a variety of metabolic traits. The variant of the first gene, *IRS1*, exhibited a complex pattern of associations: it was linked to lower body fat percentage, but surprisingly also to increased circulating fat and glucose, and to reduced levels of "good" cholesterol. The *IRS1* variant was also linked to increased insulin resistance—an adverse condition which elevates risk of type 2 diabetes and heart disease. In addition, the *IRS1* variant was associated with a higher proportion of fat surrounding the internal abdominal organs (visceral fat), which confers higher risk for disease, as compared to fat just beneath the skin (subcutaneous fat). Many of these associations, including body fat percentage and several of the metabolic traits that were analyzed, had stronger effects in men. The variant of the second gene associated with reduced body fat percentage, *SPRY2*, was linked to higher insulin sensitivity, as would be expected. While the *SPRY2* variant did not show any differences between men and women, it was linked to body fat percentage in individuals of European descent, but not in those of Indian-Asian descent.

These two genes, *IRS1* and *SPRY2*, join a growing list of genetic factors that affect body weight, body fat percentage, and other obesity indicators such as waist-to-hip ratio. The findings in this study show that the genetic contributions to body weight are complex, with specific gene variants exhibiting different influences on obesity and diabetes risk between genders, as well as among different ethnic populations. A greater understanding of these complex genetic interactions could lead to personalized intervention strategies to reduce the elevated risk of diabetes and cardiovascular disease seen in people who are overweight and obese, as well as in some people who are lean.

Kilpeläinen TO, Zillikens MC, Stančákova A, et al. Genetic variation near IRS1 associates with reduced adiposity and an impaired metabolic profile. Nat Genet 43: 753-760, 2011.

MOLECULAR MECHANISMS REGULATING FAT METABOLISM

Fat-saving Gene May Be an Achilles Heel in Efforts To Achieve Energy Balance: A molecule found in fat cells may hinder the body's ability to burn off fat, a finding that could yield new insight into the development of obesity. Normally, the body seeks a state of balance between energy consumption (eating food), energy storage (fat), and energy expenditure (burning fat to fuel activity and generate body heat). If this "energy balance" is disrupted, excess fat accumulation and obesity can result. Scientists believe they have found an unwitting contributor to this disruption in a cellular molecule called "CREB regulated transcriptional coactivator 3" (CRTC3), one of several CRTCs involved in metabolism. To mobilize stored fat for burning, the body can send signals through the nervous system to adipose (fat) cells, triggering a program of intracellular changes involved in the breakdown of fat. Interestingly, researchers found that these signals also activate CRTC3 and, surprisingly, that CRTC3 limits fat burning. Experiments in a mouse model revealed that, compared to mice possessing normal amounts of CRTC3, mice genetically engineered to lack CRTC3 had an apparent metabolic advantage—they were not only slimmer than normal mice when on a regular diet, but they also were resistant to weight gain and other negative effects of a high-fat diet, such as inflammation and insulin resistance. Intriguingly, these mice did not eat less or exercise more than their normal counterparts, nor did they appear to have problems with storing fat. Instead, the scientists found that mice lacking CRTC3 were breaking down and burning off fat as heat at a

much higher rate than usual. They appeared to do this by increasing initial fat breakdown in "white" adipose tissue, the body's most abundant form of fat tissue, and also by boosting the numbers of "brown" fat cells, which burn fat to generate heat. These experiments suggest that, normally, CRTC3 applies a "check" against the signals that stimulate fat burning, limiting their effect. Knowing, from previous research, that CRTC3 helps turn certain genes "on" or "off," the scientists performed additional experiments and discovered that, once activated, CRTC3 turns on a gene that limits fat breakdown. While these results come from studies in mice and mouse cells, it is possible that increases in CRTC3 activity relative to signals promoting fat burning could help explain disruptions in energy balance that contribute to obesity in humans. Supporting this hypothesis, the researchers found an association between a genetic variant of CRTC3, which confers an abnormally high level of CRTC3 activity, and increased risk of obesity in Mexican Americans. Armed with these new insights into the effect of CRTC3 on energy expenditure, scientists can now further explore the contribution of CRTC3 to obesity and possibly to the development of insulin resistance and type 2 diabetes.

Song Y, Altarejos J, Goodarzi MO, et al. CRTC3 links catecholamine signalling to energy balance. Nature 468: 933-939, 2010.

New Study Reveals Molecular Relationship Between Circadian Rhythm and Fat Metabolism: Results from a new study may help explain how metabolic problems develop when circadian rhythms are disrupted. In many animals, including humans, biological "circadian clocks" regulate many behaviors and bodily processes to harmonize these activities with daily, rhythmic changes in the environment, such as day/night cycles. Circadian rhythms also appear to be intricately linked with the daily regulation of metabolism. In humans, misaligning normal circadian rhythms with behaviors such as sleep and eating—for example, by working the night shift—increases vulnerability to diabetes, obesity, and other metabolic problems. However, the molecular mechanisms underlying this vulnerability are not yet clear. Because of its vital role in fat and glucose metabolism, the liver is a key target in metabolic dysfunction. Researchers have now found evidence that fat metabolism in the liver is set to a circadian rhythm by two interacting factors. One of these factors, histone deacetylase 3 (HDAC3), is an enzyme that chemically modifies structural proteins associated with DNA in a way that helps regulate gene expression (whether genes are turned "off" or "on"). When HDAC3 is recruited to sites in the genome, genes at those sites tend to be turned "off," and when it is absent, those genes are free to be turned "on."

Evidence is emerging that cells use HDAC3 as part of a nimble strategy to shift patterns of gene expression across the genome, including those important to circadian rhythms and metabolism. In the current study, researchers compared the presence of HDAC3 at sites across the mouse liver genome at two different points in the circadian cycle—once during the normal rest and fasting time for mice (day) and once during the active, feeding period (night). They found that, while HDAC3 occupied over 14,000 sites during the day, all but 120 of these sites are empty of HDAC3 at night. Chemical modifications and changes in gene expression "machinery" followed this rhythm of HDAC3 occupation in a way suggesting that gene expression at these sites was cycling from being "off" during the day to being "on" at night. In contrast, when liver cells were depleted of HDAC3, rhythmic control of gene expression at these sites was disrupted. The researchers found that the level of HDAC3 in liver cells does not itself vary significantly over the course of the day, suggesting that the rhythm of HDAC3 recruitment to the genomic sites is driven by some other factor. Indeed, they found that a "clock protein" called Rev-erbα, which is expressed in a circadian manner, is required for driving HDAC3 recruitment to its binding sites. Interestingly, the genomic sites bound by both HDAC3 and the clock protein during the day are enriched for genes involved in metabolism, particularly metabolism of lipids (chemical components of fat), including genes controlling lipid synthesis. The metabolic implications of this observation became clear when the researchers compared mouse livers depleted of HDAC3 to those with normal amounts of HDAC3. After 2 weeks of HDAC3 depletion, mouse livers had accumulated nearly 10-fold more fat than was found in livers from mice with normal amounts of HDAC3. Similar results were seen in mice lacking the clock protein: these animals had nearly twice as much liver fat as their normal counterparts.

These experiments provide an explanation for findings from other studies showing that fat synthesis in the mouse liver is higher at night, when mice are active and feeding, than during the day, when they are at rest and should be utilizing fat stores. While these studies were performed in mice, they elucidate a mechanism linking circadian rhythm with fat storage in the liver that could potentially help explain how disruption of circadian rhythm leads to metabolic dysfunction in people.

Feng D, Liu T, Sun Z, et al. A circadian rhythm orchestrated by histone deactylase 3 controls hepatic lipid metabolism. Science 331: 1315-1319, 2011.

INFLAMMATION AND OBESITY

A Double-edged Sword—The Body's Own Defenses Contribute to Insulin Resistance Associated with Obesity: New research further unraveled the complex contributions of the immune system to insulin resistance. Insulin resistance is a condition in which the body produces insulin—a hormone that helps the body use glucose for energy—but does not use it properly. Insulin resistance increases the risk for type 2 diabetes and heart disease; therefore understanding how it develops is critical toward efforts to prevent or reverse it. During excess weight gain, specific immune cells, called macrophages, migrate into and accumulate in adipose (fat) tissue and promote chronic, low-grade inflammation, which contributes to the development of insulin resistance. Although many genes and molecular pathways have been implicated in the immune response to excess weight gain, how macrophages, and other immune cells including certain T cells, promote inflammation and subsequent insulin resistance remains poorly understood. Several recent studies sought to elucidate how immune cells are activated in response to fat and turn on genes that lead to inflammation.

Two studies revealed new insights into how immune cells "sense" obesity. Proteins that reside on the surface of macrophages normally recognize foreign invaders in the body and initiate an immune response, which leads to inflammation. However, these proteins can also recognize molecules that are associated with excess weight gain and initiate a response that eventually leads to insulin resistance. In one study, scientists determined that a protein called Nlrp3 promotes insulin resistance, in part through recognition of a specific type of complex fat molecule called ceramide. When fed a high-fat diet, mice normally develop insulin resistance. Mice genetically engineered to lack Nlrp3, however, were protected from this effect. To investigate whether Nlrp3 played a similar role in humans, the researchers examined the responses of people who were obese with type 2 diabetes to weight loss through dietary changes and increased physical activity. They found that weight loss in these people led to reduced *Nlrp3* gene activity in fat tissue, and improved their sensitivity to insulin. The link between ceramide and insulin resistance was further explored in another study, in which researchers studied the effects of the hormone adiponectin on ceramide. Adiponectin, a circulating protein that promotes insulin sensitivity and reduces inflammation, interacts with a pair of protein partners (AdipoR1 and AdipoR2) on the surface of many types of cells throughout the body. The scientists discovered that AdipoR1 and AdipoR2 cause the breakdown of ceramide in the cell. Mice genetically engineered to produce increased levels of AdipoR1 and AdipoR2 in the liver had improved insulin sensitivity. Together, these findings suggest a central role for ceramide in the development of insulin resistance.

Other efforts uncovered the mechanisms by which immune cells turn on a program of immune response genes to initiate inflammation—what happens after immune cells sense obesity. In one study, scientists focused on understanding the role of FoxO1—a protein that can turn some genes on and off. The scientists showed that FoxO1 directly interacted with specific genes in macrophages, thereby activating a genetic program that induced inflammation. Importantly, when they reduced FoxO1 levels in mice, the researchers found that the inflammatory response, which was normally induced upon immune system stimulation, was abrogated. Another team of scientists dissected the function of a protein called Coronin 2A, finding that it acts in opposition to FoxO1; it associated with proteins that function to turn off genes in macrophages, including ones involved in the inflammatory response. However, when macrophages were stimulated, the scientists found that Coronin 2A facilitated the removal of these proteins from some of the inflammation genes, allowing them to be turned on. These studies have identified two key molecular factors that coordinate

the program of genes turned on during the macrophage inflammatory response.

Lastly, new results added information about how excess weight gain affects other immune cells in the development of insulin resistance. In addition to macrophages, another type of immune cell, the regulatory T (Treg) cell, is known to play a role in insulin resistance. Previous research found that Treg cells reside in the adipose tissue of lean mice, but not in that of overweight mice, and the presence of Treg cells in fat tissue helps to protect mice from developing insulin resistance. In a recent study, scientists found that, during excess weight gain in mice, macrophages in the adipose tissue send molecular signals that inhibit the production of Treg cells. This leads to depletion of Tregs in fat tissue in mice. To translate this finding to humans, the scientists showed that Treg cells were relatively abundant in human fat tissue from lean people, but observed a modest depletion of Treg cells in adipose tissue from obese individuals. This interaction between the two immune cells—macrophages and Treg cells—in fat tissue demonstrates a complex relationship between the immune system and the development of obesity.

These findings add key new knowledge to understanding the complicated immune response to obesity. Some of these recent results have been confirmed in humans, but additional research will determine whether the pathways studied in mice function similarly in people. These studies also suggest that numerous molecular pathways could serve as targets for the development of therapeutics aimed at reducing fat tissue inflammation, with the goal of preventing insulin resistance and other adverse health consequences of obesity.

Deiuliis J, Shah Z, Shah N, et al. Visceral adipose inflammation in obesity is associated with critical alterations in tregulatory cell numbers. PLoS ONE 6: e16376, 2011.

Fan W, Morinaga H, Kim JJ, et al. FoxO1 regulates Tlr4 inflammatory pathway signalling in macrophages. EMBO J 29: 4223-4236, 2010.

Holland WL, Miller RA, Wang ZV, et al. Receptor-mediated activation of ceramidase activity initiates the pleiotropic actions of adiponectin. Nat Med 17: 55-63, 2011.

Huang W, Ghisletti S, Saijo K, et al. Coronin 2A mediates actin-dependent de-repression of inflammatory response genes. Nature 470: 414-418, 2011.

Vandanmagsar B, Youm YH, Ravussin A, et al. The NLRP3 inflammasome instigates obesity-induced inflammation and insulin resistance. Nat Med 17: 179-188, 2011.

HOW THE BRAIN AFFECTS EATING BEHAVIOR AND METABOLISM

A Gut Feeling in the Brain—How the Hormone GLP-1 Signals the Brain To Reduce Food Intake and Body Weight: Researchers gained new insights into the body's control of eating with discoveries about the signals sent by a powerful molecule, GLP-1, to cells in the brain—and in particular, a part of the brain that has a direct line of communication with the gut. The body produces GLP-1 primarily in the brain and in the intestines. At meal time, GLP-1 responds to the influx of food by triggering the beta cells of the pancreas to produce insulin, which then prompts various cells in the body to take up sugar. Because of GLP-1's role in balancing blood sugar levels, scientists have developed medications, currently available, which mimic or increase GLP-1 activity as a means of treating type 2 diabetes. GLP-1 also functions to help people feel full longer, and as a result, eat less. A team of researchers recently investigated how GLP-1 exerts its effects on brain cells in rats. Based on knowledge of GLP-1's action in beta cells, the researchers focused on three signaling proteins that they thought might respond to GLP-1 in the brain. These proteins are known by their acronyms, PKA, AMPK, and MAPK—with the "K" in each standing for a type of chemical-tagging activity (kinase) common to proteins that relay important signals within cells. To facilitate their studies, the researchers used a particularly stable version of GLP-1 (called Exendin-4). They administered it directly to the rats' brains, and found that it modulated the activity of each of these signaling proteins. The rats also lost weight. With a machine the scientists refer to as a "feedometer," which recorded how much the rats were eating every minute, the researchers discovered that administering the stable version of GLP-1 into the rats' brains caused them to eat fewer meals, although the size of each meal did not change. This finding likely explains why the rats

lost weight. It is also intriguing because previous research had shown that GLP-1 administered elsewhere in the body has a different, but complementary, effect: it does not change the number of meals but does reduce the amount of food eaten in each. With more precise experiments, the researchers were able to pinpoint a key region of the brain that responds to GLP-1. This region is within an area of the brain that can communicate with the digestive tract, by sending signals through nerves that reach from the brain to the gut and back. These findings may lead to the development of new drugs that target GLP-1 signaling in the brain.

Hayes MR, Leichner TM, Zhao S, et al. Intracellular signals mediating the food intake-suppressive effects of hindbrain glucagon-like peptide-1 receptor activation. Cell Metab 13: 320-330, 2011.

A Protein in the Brain Regulates Fat Tissue Composition in the Body: Researchers have discovered that in rats, a protein in the brain determines the makeup of fat tissue and influences body weight, physical activity, and metabolism. For decades, scientists have known that damage to the hypothalamus—a part of the brain that functions to connect the nervous system to the endocrine system—leads to changes in hunger, satiety, and physical activity. These changes alter the balance between calories (energy) taken in and calories burned, or energy balance. The reasons for these changes, however, have remained unclear. Neuropeptide Y (NPY), a protein produced in different regions of the hypothalamus, is known to influence energy balance, but its function in a specific region, called the dorsomedial hypothalamus (DMH), has not been defined. To address this question, research scientists depleted NPY protein levels in the DMH of rats and examined the animals' body weight, fat composition, and metabolism. Lower NPY levels in the DMH led to reduced weight and decreased amounts of inguinal fat—a specific fat depot in the lower abdomen. When the researchers looked carefully at the cellular makeup of the inguinal fat tissue, they discovered a change in its composition. Typically, fat tissue under the skin consists largely of "white fat" cells, which store fat molecules, called lipids. Another type of fat tissue, called "brown fat," actually burns calories in order to generate heat. Reduction of NPY in the DMH led to a loss of white fat and the development of active brown fat in the inguinal tissue. The researchers also found that genes involved in breaking down lipids were turned on in the inguinal fat tissue. These effects were reduced when, prior to depleting NPY, the scientists injected a chemical into inguinal fat to destroy the nerve connections that mediate the DMH signals. In addition, when NPY levels were reduced in the rats' DMH, the scientists observed increased physical activity, energy expenditure, and body heat production in response to cold temperatures. To further understand how NPY affects obesity, rats were fed a high-fat diet, which led to weight gain, increased feeding and accumulation of fat, and increased insulin resistance (a condition associated with diabetes and prediabetes), in rats that had normal levels of NPY. Reduction of NPY in the DMH, however, lessened all of these effects of high-fat diet consumption, supporting a role for NPY in diabetes risk and obesity. These findings suggest that normally, NPY in the DMH region of the brain blocks the formation of brown fat, promotes weight gain and inactivity, and slows metabolism. This study thus adds new insights into the complicated connection between the brain and energy balance. If NPY is found to have a similar function in people, it could provide a molecular target for strategies to address obesity and associated conditions, such as type 2 diabetes.

Chao PT, Yang L, Aja S, Moran TH, and Bi S. Knockdown of NPY expression in the dorsomedial hypothalamus promotes development of brown adipocytes and prevents diet-induced obesity. Cell Metab 13: 573-583, 2011.

To Eat or Not To Eat—How Bariatric Surgery for Obesity Affects the Brain: Used for treating extreme obesity, gastric bypass surgery not only changes the digestive tract, but it also appears to affect the brain in ways that reduce the appeal of high-calorie food, as researchers discovered from brain imaging studies. Gastric bypass surgery leads to substantial weight loss by making the stomach smaller and by routing food on a shortcut through the small intestine to bypass an area that would otherwise absorb some of the calories. Yet, these changes do not appear to account for all of the weight loss.

Intriguingly, this surgery may also lead to changes in the brain. While people who lose weight from dieting often report an increase in appetite that makes it hard to keep the weight off, individuals who lose weight

from gastric bypass surgery do not seem to have the same increased desire to eat. To better understand how the surgical procedure affects the brain, researchers recruited people who were planning to have bariatric surgery, performed brain imaging (functional magnetic resonance imaging) on the volunteers 1 month before and 1 month after surgery, and compared the results. The volunteers, 10 women from diverse racial and ethnic groups, were all extremely obese prior to surgery. During each imaging session, the scientists showed the volunteers pictures of calorie-dense foods, such as pizza and cake; lower-calorie foods, such as raw vegetables; and, as a control, office supplies. They also provided recordings so that the study volunteers would hear such tempting phrases as "chocolate brownie," along with words for the other items. The brain scans revealed significant differences pre- and post-surgery. Although the pictorial and verbal food cues activated a number of regions of the brain, surgery dampened these effects, most noticeably reducing brain responses to calorie-dense foods. Moreover, the largest changes were in areas of the brain known to process rewarding experiences and pleasure-seeking behavior, such as the decision to eat highly appetizing food. When asked how they felt in response to the pictures and verbal descriptions of foods, the volunteers reported less of an inclination to eat, particularly calorie-dense foods, after surgery. Fortunately, their interest in eating vegetables did not diminish to the same extent.

This study shows that gastric bypass surgery affects brain activation and reduces the desire to eat high-calorie foods. The researchers hypothesize that one way in which surgery may have these effects could be through changes in various signaling molecules in the body that are known to influence appetite. With further research, scientists may elucidate the biological mechanisms for these effects of surgery, and potentially develop new medications to achieve the same results.

Ochner CN, Kwok Y, Conceição E, et al. Selective reduction in neural responses to high calorie foods following gastric bypass surgery. Ann Surg 253: 502-507, 2011.

It's All (Well, Partly) in Your Head—The Brain and Metabolism: Studies from several laboratories are bringing into greater focus the critical impact of the brain on regulation of body weight, and considerable evidence suggests that signals from the central nervous system also have important effects on glucose levels via the liver and other tissues. New research shows that the brain exerts its influence on glucose levels and body weight through several distinct neural and hormonal pathways, with implications for diabetes and obesity therapies.

For example, the hormone leptin—best known for its appetite-suppressing action—can also normalize glucose levels when delivered into the brains of rats with uncontrolled diabetes. Recently, in experiments in rats, researchers found that this was the result of a profound drop in the amount of glucose released into the bloodstream by the liver, as well as an increase in glucose uptake by muscle and other tissues. They found that these effects did not rely on the pancreatic hormone insulin, which lowers blood glucose through effects on liver and other tissues, and leptin's actions also did not rely entirely on reduction of glucagon, the pancreatic hormone which signals the liver to release glucose. Thus, this study helps define a novel mechanism by which leptin action in the brain can modulate glucose levels independently of these two major glucose-regulating hormones. Because this work defines an insulin-independent mechanism by which the body affects blood glucose levels, the findings may have implications for treating both major forms of this diabetes.

Another group of researchers has helped define the role of a protein called the melanocortin-4 receptor (MC4R) in controlling the liver's uptake and secretion of glucose. A mutation in the *MC4R* gene is known to cause severe obesity in humans. Mice lacking MC4R are also severely obese, with greatly elevated blood glucose and insulin levels. In studying these mice, the researchers tested the effects of restoring MC4R function only to a subset of nerve cells that usually contain MC4R; this subset is referred to as cholinergic neurons based on the type of signaling molecule (neurotransmitter) they use. Although no other tissues in the mice contained MC4R, blood glucose and insulin levels were normalized, the former partly through suppression of liver glucose production. These animals were slightly less obese than those without any MC4R at all, and further experiments showed that the modest effects on body weight likely resulted from increased calorie burning (energy expenditure), although the

mice still consumed more food than normal mice. Interestingly, previous research had shown that MC4R in other types of brain cells does affect food intake. This study therefore adds to growing evidence that MC4R has independent effects on weight and glucose levels—information that will be useful in attempts to develop obesity therapeutics targeting MC4R.

Similarly, another research team identified a key glucose modulating role for a group of nerve cells that use a different receptor protein (a serotonin receptor) and neurotransmitter. Working in mouse models, they found that these nerve cells, which are located in the hypothalamus—a part of the brain that has important effects on appetite and energy regulation in the body—also help control the liver's response to insulin.

Intriguingly, the hypothalamus contains nerve cells that can "sense" glucose in a similar fashion to pancreatic beta cells. Another research team investigated a subset of these nerve cells to see if they play a role in regulating blood glucose levels in the body. Because the nerve cells they studied are directly stimulated by glucose, the researchers developed experimental methods in mice to make the nerve cells more sensitive so that even low levels of glucose stimulate them to fire, or less sensitive, firing only when glucose reaches higher than normal levels. These experiments helped identify molecules in the nerve cells important for glucose sensing. Additionally, they found that the effects extended beyond the brain: making the nerve cells more sensitive led to lower blood glucose levels, while lower sensitivity led to higher glucose levels, indicating that impulses from these nerve cells have a key role in modulating blood glucose levels.

Each of these discoveries helps in understanding the way the brain affects metabolic processes elsewhere in the body, and each represents a potential target for intervention to restore healthy glucose levels in people with diabetes.

German JP, Thaler JP, Wisse BE, et al. Leptin activates a novel CNS mechanism for insulin-independent normalization of severe diabetic hyperglycemia. Endocrinology 152: 394-404, 2011.

Rossi J, Balthasar N, Olson D, et al. Melanocortin-4 receptors expressed by cholinergic neurons regulate energy balance and glucose homeostasis. Cell Metab 13: 195-204, 2011.

Xu Y, Berglund ED, Sohn J-W, et al. 5-HT2CRs expressed by pro-opiomelanocortin neurons regulate insulin sensitivity in liver. Nat Neurosci 13: 1457-1459, 2010.

Kong D, Vong L, Parton LE, et al. Glucose stimulation of hypothalamic MCH neurons involves K(ATP) channels, is modulated by UCP2, and regulates peripheral glucose homeostasis. Cell Metab 12: 545-552, 2010.

RESEARCH TO FIGHT CHILDHOOD OBESITY

Examining How Maternal Glucose Levels May Influence Childhood Obesity: New studies are providing insight into how nutritional exposures in the womb may affect children's risk for overweight and obesity as they grow. Concerns have been rising about the effects on offspring of gestational exposure to elevated maternal blood glucose levels. Previous research had established that maternal diabetes during pregnancy not only increases likelihood of complications during gestation and delivery, but that it also increases risk of obesity and type 2 diabetes in the offspring. However, more recently, a major clinical study showed that elevated maternal blood glucose levels below those diagnostic of gestational diabetes still incurred risk for serious pregnancy, birth, and neonatal complications. Now, researchers are trying not only to better understand these short-term risks, but also to ascertain whether even moderately elevated maternal blood glucose levels affect future obesity risk in offspring.

Two recent studies tackling this question have found a positive correlation. In one study, researchers recruited over 260 women, a subset of over 1,000 who had participated in a large pregnancy clinical study and whose babies were now toddlers. They looked to see if there was a relationship between maternal blood glucose levels in women not diagnosed as diabetic during pregnancy and their child's body mass index (BMI) at 3 years of age. The study results suggest that high maternal glucose levels during pregnancy correlate with increased risk of overweight and obesity in the children. Another research team pursued this question in 27 older children, between 5 and 10 years of age, whose mothers' blood glucose levels during pregnancy ranged from low to diabetic. In this study,

not only was the children's body composition—both fat and lean mass—determined, but also their resting energy use and activity levels, which could affect their body composition, particularly their amount of body fat. The results suggest that the higher a mother's glucose levels during pregnancy, the more likely the child will have both higher fat and lean mass, and that this correlation may be independent of how active the child is, their energy use at rest, and their diet. These studies were small and had other limitations, so additional research is needed to understand the long-term effects of prenatal exposure to elevated maternal glucose levels on children's risk of obesity. Nonetheless, both studies suggest avenues for further investigation toward the goal of promoting healthy outcomes for the next generations.

Chandler-Laney PC, Bush NC, Rouse DJ, Mancuso MS, and Gower BA. Maternal glucose concentration during pregnancy predicts fat and lean mass of prepubertal offspring. Diabetes Care 34: 741-745, 2011.

Deierlein AL, Siega-Riz AM, Chantala K, and Herring AH. The association between maternal glucose concentration and child BMI at age 3 years. Diabetes Care 34: 480-484, 2011.

Lifestyle Intervention Program Targeting Obesity Shows Promise in Ethnically Diverse Children: New research has shown that an intensive, family-based lifestyle intervention program can lead to sustained reductions in body weight and indicators of diabetes risk in ethnically diverse children. Because the high rate of childhood obesity and overweight has been a challenging problem, many previous studies had focused on body weight management through lifestyle intervention. While some of these studies led to reductions in body weight, they were limited in scope because they often involved small numbers of predominantly Caucasian, middle-class participants who were not as obese as the children in the current study, and limited follow-up times after the intervention.

In order to extend and broaden the scope of previous research, scientists in this intervention study included larger cohorts of ethnically diverse (African American and Hispanic) inner-city children from predominantly lower-income families—populations that tend to be at high risk for obesity and overweight. Study cohorts included children, ages 8 to 16, who were obese, as defined by a body mass index (BMI, a measure of weight relative to height) at or above the 95th percentile. Participants were randomly assigned to either an intervention or control group. The intervention group received an extensive family-based program that included: a twice-weekly exercise regimen of intense aerobic games and other physical activities (*e.g.*, obstacle courses, basketball, and flag football); nutrition education that promoted healthy foods and moderate consumption; and behavior modification instruction that provided training in self-awareness and goal-setting. Children in the intervention group were also encouraged to maintain a healthy lifestyle after the program was completed. In contrast, the control group received general information on diet and exercise, along with psychosocial counseling, every 6 months for the duration of the year. Although the active portion of the study ended after 12 months, researchers followed all participants for an additional 12 months to determine longer-term effectiveness of the interventions. Evaluation measures included physical traits (height, weight, BMI, percent body fat, blood pressure) and levels of blood components (insulin, glucose, circulating fats, and cholesterol).

The results demonstrated that the average BMI in the intervention group was reduced within 6 months and sustained for 24 months—1 year after the end of the intervention program. In addition, significant reductions in insulin resistance—a measure of the body's inability to utilize the hormone insulin to promote the uptake of sugar, and an indicator of risk for diabetes—were also observed at 24 months. The results from this study indicate that intensive lifestyle intervention programs can sustainably lower excess body weight and improve other health measures in children from diverse ethnic and socioeconomic backgrounds, potentially leading to a reduced burden of obesity-related health problems into adulthood.

Savoye M, Nowicka P, Shaw M, et al. Long-term results of an obesity program in an ethnically diverse pediatric population. Pediatrics 127: 402-410, 2011.

It All Adds Up—New Mathematical Model Helps Explain Why Dietary Strategies Have Not Worked Well for Many People

Researchers have found that the widely accepted dietary paradigm for weight loss—that reduction of 3,500 calories will shed one pound of weight—is incorrect, and have developed a mathematical model (and an accompanying online weight simulation tool) that more accurately predicts weight loss for adults. The commonly held belief that eating 3,500 fewer calories, or burning them off exercising, will always result in a pound of weight loss assumes that all people respond to caloric change in the same way. A recent study conducted by scientists in the NIDDK Intramural Research Program has challenged this static model and shown it to be overly simplistic. Many diets fail because people have unreasonable expectations based on the static model: they expect to see results rapidly, and feel discouraged when weight loss slows over time despite adherence to a specific diet. The new model developed by this research team reveals that this pattern of anticipated weight loss is unrealistic, leading many people to abandon their diet and exercise strategies.

In order to address complex, multi-faceted health conditions, a range of conceptual and technological approaches must be employed by scientists. Dr. Kevin Hall, trained physicist and research scientist at the NIDDK, decided to tackle the health burden of obesity by utilizing his strong mathematical skills to develop a more comprehensive, and much more realistic, model for weight loss and metabolism. Computer-based simulations developed by his lab more accurately reflect changes in a person's body during weight loss by taking into consideration differences between people, such as gender, age, height, weight, amount of body fat, and resting metabolic rate. The team's complex mathematical "dynamic" model and internet-based weight simulation tool (found at *http://bwsimulator.niddk.nih.gov*) incorporates these various parameters; the model also accounts for changes in metabolism during weight loss, and the variation in these changes among people. "This research helps us understand why one person may lose weight faster or slower than another, even when they eat the same diet and do the same exercise," explains Dr. Hall. "Our computer simulations can then be used to help design personalized weight management programs to address individual needs and goals."

To test their model, the scientists compared expected weight changes to actual changes in people. They found that the new model more accurately predicted weight loss, suggesting that many factors must be integrated to fully understand an individual's response to diet and exercise. These simulations revealed many physiological complexities associated with weight loss. For example, the team found that people's bodies adapt slowly to changes in dietary intake. They also found that heavier people can expect greater weight change with the same change in diet, though reaching a stable body weight will take them longer than people with less fat. The previous static model overestimated weight loss because it failed to account for how metabolism changes during weight loss.

The model makes specific predictions about weight loss, as illustrated by making assumptions for an average overweight adult. In this case, for every pound of weight loss desired, 10 calories per day must be permanently cut from the current intake. At that rate, it will take about 1 year to achieve half of the total weight loss, and almost all of the weight loss will have occurred by 3 years. Researchers can use the web simulation tool to plan for an initial phase of more-rapid weight loss followed by a weight maintenance phase. "By using our model to track progress, clinicians can help people re-evaluate their goals and ability to achieve them at the pace they want," Dr. Hall said. "It's a good reality check for how long weight loss takes, and what changes in eating and exercise are required to achieve and maintain goal weight."

The effective use of mathematical modeling to address real-world health problems—in this case obesity—highlights the need to explore inventive research directions. "This research illustrates how the interdisciplinary skills of NIH scientists, like a physicist doing obesity research, can help lead to innovative

ways to test, understand, and treat a major public health epidemic," said NIDDK Director Dr. Griffin P. Rodgers, "Advancing research from the laboratory to the bedside enables us to make the discoveries that can better people's lives." The NIDDK has been committed to advancing research in a range of health issues through computational approaches. For example, scientists in the NIDDK's Laboratory of Biological Modeling pioneered the field of computational neuroscience. By investigating the behavior of oscillating signals, these scientists have applied modeling to research fields like neuronal signaling and insulin secretion from the beta cells of the pancreas.

Despite its validity in a controlled research setting, the computer simulation of metabolism is intended to be a research tool, not a specific weight-loss guide for the public. The computer program can run simulations for changes in calories or exercise that would never be recommended for healthy weight loss, and people should consult with their physician prior to embarking on a diet plan. Additionally, the researchers point out that their current mathematical model was developed for adults, and would not predict weight change in children and adolescents because it does not account for biological changes associated with growth.

Current research by Dr. Hall's team seeks to improve the computational modeling tool to make it more useful for a variety of applications. To more rigorously test the model, Dr. Hall and his team are taking advantage of NIDDK's Metabolic Clinical Research Unit—a state-of-the-art facility that allows researchers to carefully measure energy intake (how many calories individuals eat) and expenditure (how many calories people burn to fuel basic life functions and physical activity). Efforts are also underway to use and validate this computational tool in clinical trials. The model is currently being tested in an NIDDK-funded clinical trial aimed at understanding links between specific foods and human physiology, including brain reward pathways. The trial will provide metabolic data from participants undergoing weight loss, which will then be used to test the model through personalized computer simulations.

The new model developed by Dr. Hall and his colleagues shows that weight loss in adults happens slowly over longer periods of time than previously expected. This finding could help explain why many dieters observing initial weight loss relax their diets, only to find that the weight comes back due to altered metabolism. The model can also be used to help simulate potential effects of policy changes aimed at addressing obesity. Dr. Hall and his team hope to use the knowledge gained from developing the model and from clinical trials in people to refine the tool so everyone can develop a healthy and realistic personal strategy for long-term weight management.

Hall KD, Sacks G, Chandramohan D, et al. Quantification of the effect of energy imbalance on bodyweight. Lancet 378: 826-837, 2011.

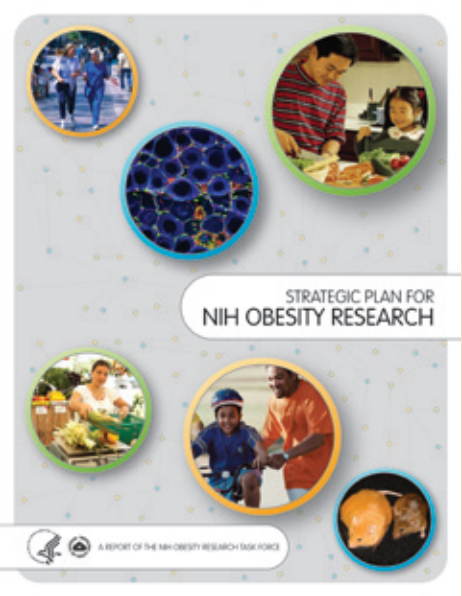
Strategic Plan for NIH Obesity Research

In 2011, the NIH published an updated *Strategic Plan for NIH Obesity Research*. The new *Strategic Plan* reflects the exciting scientific advances and opportunities that have emerged in the years since the NIH published its first strategic plan for research on this major public health challenge. Obesity is a major contributor to type 2 diabetes, cardiovascular disease, many forms of cancer, and numerous other diseases and conditions in adults and children. Because obesity is a multi-faceted problem, the new *Strategic Plan* outlines a multi-faceted research agenda to illuminate the causes and consequences of obesity, develop and evaluate diverse prevention and treatment strategies, explore ways to implement and scale up promising approaches, and provide an evidence base to inform policy-making. Integral to all areas of the *Strategic Plan* are studies to identify and reduce health disparities, including research focused on populations at disproportionate risk for obesity and its serious health consequences. Also emphasized is translational research—bridging scientific discovery to improvements in public health.

The *Strategic Plan* is framed around the following overarching themes:

- Discover fundamental biologic processes that regulate body weight and influence behavior
- Understand the factors that contribute to obesity and its consequences
- Design and test new interventions for achieving and maintaining a healthy weight
- Evaluate promising strategies for obesity prevention and treatment in real-world settings and diverse populations
- Harness technology and tools to advance obesity research and improve health care delivery
- Facilitate integration of research results into community programs and medical practice

The trans-NIH Obesity Research Task Force developed the *Strategic Plan* with crucial input from researchers across the nation, professional and other health-focused



organizations, health care providers, and the public. As one of the lead Institutes on the Task Force, the NIDDK had a major role in the development of the *Strategic Plan*. Co-leading the Plan's development with the NIDDK were the National Heart, Lung, and Blood Institute, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, and the National Cancer Institute; and many other NIH components participated.

Importantly, the *Strategic Plan* is intended to be dynamic. NIH research planning will continue to build on emerging discoveries and knowledge, catalyze the development of new and more effective obesity prevention and treatment approaches and expand those that work, so that people can look forward to healthier lives.

Two versions of the *Strategic Plan for NIH Obesity Research* are available: a full version targeted to the scientific community, and a non-technical summary. Both can be accessed on the NIH web-site at *http://obesityresearch.nih.gov/About/strategic-plan.aspx*