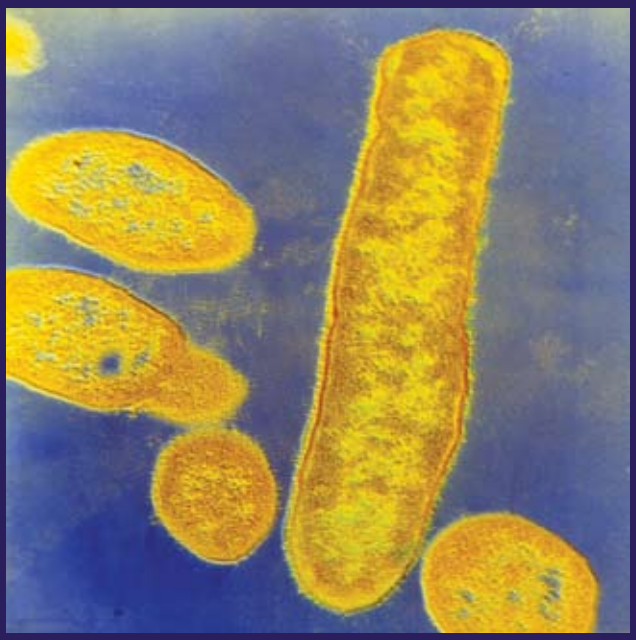

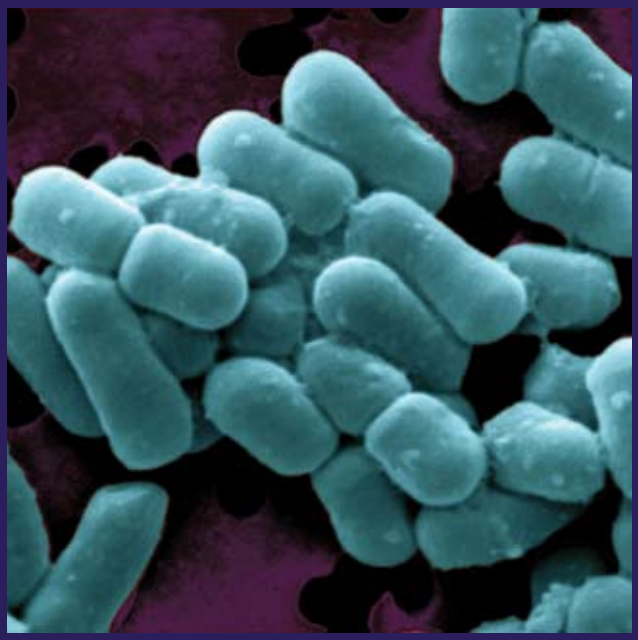

In addition to genetics and lifestyle, researchers supported by the NIDDK have found an important "insider" that also contributes to human obesity: the trillions of bacteria and other tiny organisms (microbes) residing in the human gut. Recent studies detailed in this chapter show the potent effects that certain bacteria have on their host's nutrient absorption and metabolism, which contribute to obesity. For example, researchers have discovered that obese and lean individuals differ in their relative abundance of intestinal bacteria with different energy-harvesting abilities from the Bacteroidetes (top image) and Firmicutes (bottom image) bacterial divisions.

Top image credit: CNRI/Photo Researchers Inc.

Bottom image credit: Scimat/Photo Researchers Inc.

Obesity

Obesity has risen to epidemic levels in the U.S. Obese individuals 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.[1,2,3] Furthermore, while obesity and overweight have risen in the population in general, the greatest increases observed over approximately the past two decades have been in the prevalence of extreme obesity; those who are severely obese are most at risk for serious health problems.[4] Levels of childhood overweight have also escalated in the past several decades; approximately 17 percent of children and teens ages 6 through 19 are now overweight.[1,2,5,6] The levels of pediatric overweight have ominous implications for the development of serious diseases both during youth and later in adulthood. Overweight and obesity also disproportionately affect racial and ethnic minority populations, and those of lower socio-economic status.

The increased prevalence of obesity in the U.S. is thought to result from the interaction of genetic susceptibility with behavior and factors in the environment that promote increased caloric intake and sedentary lifestyles. Thus, the NIDDK supports a multidimensional research portfolio on obesity, ranging from basic studies to large clinical trials. Examples include: investigations to elucidate the hormones and other signaling molecules that influence appetite and energy expenditure, and that link obesity to type 2 diabetes and other adverse health conditions; research on the role of inflammation in obesity-associated health problems; studies of the role of gut bacteria in obesity; exploration of genetic factors that predispose individuals to obesity; research on nutrition and physical activity; the development and testing of modifications to environmental factors in schools, the home, and other settings as strategies for obesity prevention; and research on bariatric surgery as a treatment for severe obesity. The NIDDK additionally supports studies of eating disorders that are associated with obesity in some people.

Highlights of recent advances from NIDDK-supported research on obesity are provided in this chapter. To help bring the results of research to the public and health care providers, the NIDDK also sponsors education and information programs. Given the importance of the obesity epidemic as a public health problem, and its relevance to the mission of the NIDDK, the Institute has played a leading role in the NIH Obesity Research Task Force. Established by the NIH Director and co-chaired by the Directors of the NIDDK and the National Heart, Lung, and Blood Institute, the Task Force includes representatives from these and numerous other NIH Institutes, Centers, and Offices. With extensive input from external scientists and the public, the Task Force developed the *Strategic Plan for NIH Obesity Research*, published in August 2004 *(http://obesityresearch.nih.gov/About/strategic-plan.htm)*. The NIH is currently

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

[2] Ogden CL, et al: JAMA 295: 1549-1555, 2006.

[3] National Center for Health Statistics. Obesity Among Adults in the United States—No Significant Change Since 2003-2004. Data Brief Number 1. Hyattsville, MD: Public Health Service. 2007.

[4] Flegal KM, et al: JAMA 288: 1723-1727, 2002; Flegal KM and Troiano RP: Int. J. Obes Relat Metab Disord 24: 807-818, 2000; Freedman DS, et al: JAMA 288: 1758-1761, 2002.

[5] National Center for Health Statistics. Chartbook on Trends in the Health of Americans. Health, United States, 2006. Hyattsville, MD: Public Health Service. 2006.

[6] This document uses the terms overweight and obesity interchangeably for children and adolescents because there is no generally accepted definition for obesity, as distinct from overweight, in this age group.

supporting a spectrum of research studies consistent with the recommendations of the *Strategic Plan.*

WEIGHT REDUCTION IN INDIVIDUALS WITH TYPE 2 DIABETES

First Year of the Look AHEAD Trial Yields Encouraging News for Patients with Type 2 Diabetes: After 1 year, individuals in the Look AHEAD (Action for Health in Diabetes) clinical trial who were assigned to an intensive lifestyle intervention had significantly greater improvement in health measures than did individuals receiving diabetes support and education alone. The Look AHEAD trial enrolled over 5,000 patients to determine whether the intensive lifestyle intervention could impact the long-term health of overweight and obese adults with type 2 diabetes. Half of the patients received this intervention, which consisted of weight loss through decreased calorie consumption and increased physical activity. This group of patients also received counseling through weekly individual or group meetings with a team of specialists. The diabetes support and education intervention consisted of three diabetes education sessions held throughout the year. Assessments of the use of diabetes, blood pressure, and cholesterol medication; weight; blood sugar (glucose) levels; blood pressure; cholesterol levels; kidney function; presence of the metabolic syndrome; and other measures were completed for all patients at the beginning of the trial and after 1 year of the interventions. The Look AHEAD trial was designed to follow the participants for up to 11.5 years, if specific criteria during the first year were met. These included a greater than 5 percent difference in average weight change between the two intervention groups and a greater than 5 percent loss in average weight over 1 year in the intensive lifestyle intervention group. Both of these criteria were exceeded. In addition to the greater weight loss in the patients receiving the intensive lifestyle intervention, these individuals also had lower blood glucose levels; decreased use of medications for diabetes, blood pressure, and cholesterol; and improved cholesterol and blood pressure levels. As the Look AHEAD trial continues over the next several years, it will provide valuable information regarding the use of an intensive lifestyle intervention for reaching and maintaining a weight loss goal in people with type 2 diabetes, and whether the promising results seen thus far lead to long-term health benefits associated with weight loss.

Look AHEAD Research Group, Pi-Sunyer X, Blackburn G, Brancati FL, Bray GA, Bright R, Clark JM, Curtis JM, Espeland MA, Foreyt JP, Graves K, Haffner SM, Harrison B, Hill JO, Horton ES, Jakicic J, Jeffery RW, Johnson KC, Kahn S, Kelley DE, Kitabchi AE, Knowler WC, Lewis CE, Maschak-Carey BJ, Montgomery B, Nathan DM, Patricio J, Peters A, Redmon JB, Reeves RS, Ryan DH, Safford M, Van Dorsten B, Wadden TA, Wagenknecht L, Wesche-Thobaben J, Wing RR, and Yanovski SZ: Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: One-year results of the Look AHEAD trial. Diabetes Care 30: 1374-1383, 2007.

GUT BACTERIA AND OBESITY

New Insights on the Relationship Between Obesity and Gut Bacteria: While genetics and lifestyle can conspire to promote obesity, an additional potential accomplice has emerged from recent research: the bacteria and other tiny organisms (microbes) that normally reside in the gut. Studies are revealing how some of these trillions of microbes may not only contribute to a flood of extra calories, but also modulate the biologic pathways that regulate metabolism and whether calories are burned or stored as fat.

Able to digest many dietary components that the body's own intestinal cells can't, gut microbes offer extra energy from food in exchange for a home in the gut. However, some may provide more food energy than others in the form of calories. By analyzing the genomes of these microbes, referred to collectively as the "microbiome," scientists discovered that the relative abundance of two major types of gut bacteria differ between lean and obese mice. They additionally found, through genomic and biochemical analyses, that these types of gut bacteria differ in their capacity to harvest energy from food. Those more prevalent in the obese mice are better able to extract calories—and potentially provide too many extra calories to their mouse "hosts." In a parallel study in humans, the scientists found that the relative abundance of these types of gut bacteria also differs between lean and obese people. Additionally, when the obese study volunteers lost weight by dieting, the relative proportions of these bacteria in their guts also changed. To further explore these effects, the researchers turned again to mice. They raised several

mice in "germ-free" conditions so the mice would lack normal gut bacteria and then gave them gut bacteria from other (donor) mice. No longer germ-free, the mice who received gut bacteria from obese donors gained significantly more body fat over the next two weeks than mice who received gut bacteria from lean donors.

In another set of experiments in mice, scientists found that the bacteria that live in the gut also engage in a form of home remodeling, at the molecular level. They reduce the amounts of some native mouse proteins that would otherwise keep body weight down. The researchers first found that germ-free mice do not gain as much weight on a high-fat "Western diet" as do mice that have normal gut bacteria. They then showed that mice raised germ-free have increased activity of a protein called AMPK, which helps burn fat in muscles and the liver. Building on previous research, they found that gut microbes may also contribute to diet-induced obesity by reducing levels of another mouse protein, called Fiaf, as well as mouse proteins that are regulated by Fiaf, which results in enhanced fat storage. Finally, using an implantable device in the mice to track locomotion, the scientists observed that mice raised without gut microbes move more, and thus may be burning more calories than mice with gut bacteria.

These studies show that the gut's resident microbes affect not only the amount of calories obtained from food, but also whether the calories are stored or burned. Manipulation of the composition of gut bacteria may one day be a novel approach to obesity prevention or treatment.

Bäckhed F, Manchester JK, Semenkovich CF, and Gordon JI: Mechanisms underlying the resistance to diet-induced obesity in germ-free mice. Proc Natl Acad Sci USA 104: 979-984, 2007.

Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, and Gordon JI: An obesity-associated gut microbiome with increased capacity for energy harvest. Nature 444: 1027-1031, 2006.

MOLECULAR CONTRIBUTORS TO OBESITY

A High-Fat Diet, Inflammation, and Metabolic Problems—New Insights: As scientists seek to understand how obesity causes chronic and devastating health problems, they have uncovered a convergence between inflammation and impaired response to the hormone insulin. Obesity can hinder the ability of tissues throughout the body to respond properly to insulin. Such insulin resistance is a harbinger of serious disease, including type 2 diabetes. In addition to obesity and insulin resistance, a high-fat diet has also been associated with inflammation. Recent studies are illuminating how fat co-opts the immune system to produce inflammation by affecting cells called macrophages and other inflammatory factors.

To gain insight into how fat triggers inflammation, and consequently insulin resistance, one research group sought clues from a different biological process: fighting infection. Many bacteria are coated with a fat-containing substance which activates inflammatory pathways, specifically those controlled by a protein called TLR4. Perhaps, then, fatty acids from food might also incite inflammation via TLR4. To test this hypothesis, the scientists began by comparing macrophages and fat cells from normal mice to those from mice lacking TLR4 (due to genetic mutation). They found that fatty acids induced molecular changes associated with inflammation in both the macrophages and fat cells from normal mice, but not in those lacking TLR4. These findings demonstrated the need for TLR4 in this process. Bringing obesity into the picture, the scientists then discovered that there is more TLR4 in fat tissue from obese mice than from lean mice. Exploring the effects of dietary fat, they found that nutritional fatty acids, when injected into mice, elicited signs of inflammation and insulin resistance, but these were reduced in mice lacking TLR4. Further experiments in the mice also suggested that TLR4 may play a role in the metabolic problems associated with a high-fat diet. Thus, the investigators discovered that a protein known for its beneficial function in fighting bacterial infection, TLR4, may also play an adverse role in metabolism as a link among fat, inflammation, and insulin resistance.

The focus of another group of scientists was a protein called Cap, which earlier studies had suggested may play a role in insulin action. To better understand this protein, the scientists generated mice that lacked the Cap protein, and fed them a high-fat diet. In normal mice, a high-fat diet impedes the ability of muscle, liver, and fat tissue to respond properly to insulin. Muscles do not take up glucose sufficiently from the bloodstream; the liver continues producing excess glucose; and fat

tissue is impaired in its processing of fatty acids—resulting in too much fat in the blood. In mice lacking the Cap protein, however, measures of glucose uptake and production, fatty acids in blood, and other factors indicated protection from insulin resistance. This result was surprising and intriguing, in light of earlier studies of the Cap protein. Pursuing a potential role for Cap in the inflammation associated with insulin resistance, the investigators further examined mice fed a high-fat diet. They observed that many fewer macrophages had infiltrated the fat tissue of Cap-deficient mice, as compared with normal mice. Additional experiments showed that isolated macrophages, normally mobile, are less able to migrate when deficient in Cap protein. Finally, the investigators generated mice that lacked Cap protein only in their macrophages and other immune cells, but not elsewhere in the body. They did this by transplanting bone marrow from Cap-deficient mice into normal mice whose own immune systems had been eradicated. (Although other types of immune cells derive from bone marrow, the scientists pointed out that only macrophages are thus far known to play a role in insulin resistance.) The transplanted macrophages, absent the Cap protein, were able to protect the normal mice from insulin resistance induced by a high-fat diet. Thus, the Cap protein is used in macrophages to modulate inflammation as an unhealthy response to a high-fat diet.

These studies shed new light on the pathways leading from a high-fat diet and obesity to inflammation and then to insulin resistance. Additionally, they open new avenues for further research into the complex biological origins of obesity-related metabolic disease, which may inform the development of new therapeutic approaches.

Lesniewski LA, Hosch SE, Neels JG, de Luca C, Pashmforoush M, Lumeng CN, Chiang SH, Scadeng M, Saltiel AR, and Olefsky JM: Bone marrow-specific Cap gene deletion protects against high-fat diet-induced insulin resistance. Nat Med 13: 455-462, 2007.

Shi H, Kokoeva MV, Inouye K, Tzameli I, Yin H, and Flier JS: TLR4 links innate immunity and fatty acid-induced insulin resistance. J Clin Invest 116: 3015-3025, 2006.

Blood Protein Warns of Hidden Belly Fat and Disease Risk: People with excess deep-belly fat are known to be at increased risk for cardiovascular disease and type 2 diabetes. Now scientists have found that this type of fat, compared to other types, produces higher levels of a protein that can be detected in the blood. The protein may serve as a simple indicator for deep visceral fat and disease risk. In recent years, scientists supported by the NIDDK have been exploring the unexpected complexity of the molecule retinol-binding protein 4 (RBP4), once thought to have the sole purpose of ferrying vitamin A (retinol) through the bloodstream. The researchers showed that it appears to affect insulin resistance, a risk factor for diabetes, in mice. In people, RBP4 is elevated in obese or diabetic individuals with insulin resistance, and it drops with exercise training or other interventions known to reverse insulin resistance.

In the new study, the scientists set out to determine if blood levels of RBP4 were directly influenced by visceral fat, which surrounds abdominal organs and has been linked to disease risk. They measured blood levels of RBP4 in 130 obese and 66 lean people. Each participant underwent a computed tomography (CT) scan to assess relative amounts of visceral fat and subcutaneous fat, which lies just beneath the skin. The researchers also analyzed RBP4 gene expression in small samples of both visceral and subcutaneous fat from each person. The scientists found that, overall, RBP4 gene expression was 5-fold higher in visceral than in subcutaneous fat. In obese people with a "visceral fat" pattern of obesity, RBP4 gene expression in visceral fat cells was 60-fold higher than in the lean group. By comparison, RBP4 expression was just 12-fold above normal in people with a "subcutaneous fat" pattern. Blood levels of RBP4 measured up to 3 times higher in obese than in lean people. Those with higher blood levels of RBP4 had more abdominal fat and lower insulin sensitivity, regardless of their age, gender or body mass index (a ratio of weight to height). Among several fat-secreted proteins now associated with insulin activity, blood concentration of RBP4 is thus far the strongest predictor of a person's visceral fat load and insulin resistance. With further study, RBP4 may serve as a convenient marker to identify patients at risk for type 2 diabetes and cardiovascular disease.

Klöting N, Graham TE, Berndt J, Kralisch S, Kovacs P, Wason CJ, Fasshauer M, Schön MR, Stumvoll M, Blüher M, and Kahn BB: Serum Retinol-Binding Protein is more highly expressed in

visceral than in subcutaneous adipose tissue and is a marker of intra-abdominal fat mass. Cell Metab 6: 79-87, 2007.

—Reprinted, in slightly modified form, from NIH Research Matters; original article by Vicki Contie published July 23, 2007.

Extending Lifespan—Effects of Insulin Signaling and the IRS2 Protein in the Brain: Recent studies are illuminating the role of a protein called IRS2 in coordinating calorie intake, physical activity, and antioxidant function to affect lifespan. This protein had been known to work with the hormone insulin in helping the body to maintain normal blood sugar levels and in modulating other aspects of metabolism. (Its name is an acronym for an "insulin receptor substrate.") In earlier experiments, researchers had found that mice completely lacking IRS2 developed high blood sugar levels, which progressed to severe type 2 diabetes at a relatively young age. These mice also had reduced brain growth. Recently, scientists examined mice that had lower-than-normal levels of IRS2 due to a genetic mutation, but were not completely IRS2-deficient. Paradoxically, the scientists found that the lifespan of these mice was 17 percent longer than their normal counterparts. Delving further into the role of IRS2 in longevity, the researchers focused on the effects of this protein in the brains of mice. Using genetic engineering, they generated mice with lower levels of IRS2 in their brains, but normal levels elsewhere in the body. These mice also had significantly longer life spans than normal mice. Thus, although some IRS2 protein in the body is necessary for health, as evident from the earlier experiments, there can be too much of a good thing: reducing signaling through the IRS2 protein in mice increases their lifespans.

In experiments to better understand this phenomenon, the scientists assessed various metabolic and other health-related factors in the mice. Among their findings, they discovered that older mice with reduced IRS2 in their brains were about twice as active as those with levels of this protein that were closer to normal. Additionally, a measure of glucose metabolism in these mice appeared to be more in the healthy range. The scientists also explored another area commonly associated with aging—antioxidants. The body produces enzymes that have antioxidant activity to help protect cells. Because reduced insulin-like signaling has been shown to increase production of these enzymes, the scientists examined a key antioxidant enzyme in the brains of their mice. Mice with reduced levels of IRS2 in their brains had more of the protective antioxidant enzyme in old age. Based on this research, the scientists suggest a potential implication for human aging. Perhaps human longevity could be extended through strategies to decrease the requirement for IRS2 signaling. Such efforts could include exercise and reduced calorie intake, which would lower the amount of insulin and IRS2 needed to process sugar from food. Interestingly, calorie restriction is associated with longevity in animals. This study thus sheds new light on the connections between aging and metabolism.

Taguchi A, Wartschow LM, and White MF: Brain IRS2 signaling coordinates life span and nutrient homeostasis. Science 317: 369-372, 2007.

Compound Improves Fitness and Survival in Overweight Mice: Two groups of researchers have shown that a naturally-occurring compound called resveratrol significantly improves health and lifespan in overfed mice. Obesity is linked to a host of health problems including type 2 diabetes and cardiovascular disease, and reduced life expectancy. A high-fat diet causes weight gain and insulin resistance in mice compared to animals eating a standard diet. As in humans, these developments shorten lifespan. The researchers found that resveratrol prevented insulin resistance in mice on a high-fat diet, and increased lifespan almost to that of control mice fed healthier food. Although one group found that resveratrol helped prevent weight gain in the mice, the other did not see a significant difference. Both groups also found that measures of physical fitness, such as motor coordination and stamina, were improved in the mice given resveratrol. Although it is not yet known whether resveratrol will have a similar effect in humans, these results suggest the possibility that a dietary supplement may one day help prevent some of the health problems associated with a high-fat/high-calorie diet.

Lagouge M, Argmann C, Gerhart-Hines Z, Meziane H, Lerin C, Daussin F, Messadeq N, Milne J, Lambert P, Elliott P, Geny B, Laakso M, Puigserver P, and Auwerx J: Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1alpha. Cell 127: 1109-1122, 2006.

Baur JA, Pearson KJ, Price NL, Jamieson HA, Lerin C, Kalra A, Prabhu VV, Allard JS, Lopez-Lluch G, Lewis K, Pistell PJ, Poosala S, Becker KG, Boss O, Gwinn D, Wang M, Ramaswamy S, Fishbein KW, Spencer RG, Lakatta EG, Le Couteur D, Shaw RJ, Navas P, Puigserver P, Ingram DK, de Cabo R, and Sinclair DA: Resveratrol improves health and survival of mice on a high-calorie diet. Nature 444: 337-342, 2006.

DETERMINANTS OF FAT FORMATION

Insights into How Fat Is Stored in the Body: Three recent studies have examined how much fat is stored in the body, what type of fat tissue is made, and where in the body the fat is stored. The findings may provide new pathways to target for therapies.

One group of researchers studied a gene, *adipose*, whose mutation led to increased fat formation in several experimental organisms. Conversely, when the researchers genetically-engineered mice to have extra copies of the *adipose* gene, and thus likely increased amounts of the protein it encodes, they observed a reduction in the storage of fat. This "adipose" protein interacts with other proteins that are involved in turning genes off, suggesting that it may inhibit fat formation by turning off genes that would promote the storage and maintenance of fat.

Another group of researchers, studying mice, identified a gene, *PRDM16*, which plays a major role in directing the development of brown fat cells. Fat cells are of two types: white fat cells, which store energy (as fat), and brown fat cells, which release energy in the form of heat. The researchers showed that expression of *PRDM16* turned on genes and activities that are characteristic of brown fat cells. Like the protein made from the *adipose* gene, the PRDM16 protein also has its effect on fat by regulating whether genes are turned on or off. Adult humans do not have much brown fat naturally, but this study of PRDM16 could have therapeutic implications as it may be possible to stimulate the formation of brown fat cells to release energy as heat, thus preventing excess fat accumulation.

In the final study, researchers genetically modified obese mice to alter where fat is stored in the body. They began with mice that are obese as a result of deficiency in the hormone leptin. In these mice, fat is stored not only in fat tissue, but also in non-fat tissues like the liver and muscle, which may lead to a number of the health problems seen in these mice, such as insulin resistance, a condition associated with type 2 diabetes. When the researchers engineered these mice to produce higher amounts of a protein called adiponectin, the excess fat was no longer stored in non-fat tissues such as the liver, but rather in fat tissue beneath the skin, resulting in even greater obesity. Despite this excess fat tissue, the mice had normal glucose and insulin levels and did not have many of the disease symptoms and morbidity associated with obesity and type 2 diabetes. This result suggests that the location of fat storage is important in how the body responds to obesity. This mouse model may be useful for further research to understand fat storage and its relation to metabolic disease.

Each of these studies contributes more knowledge to our understanding of how fat is stored in the body. This research also reveals potential new areas for the development of therapeutics to combat obesity.

Suh JM, Zeve D, McKay R, Seo J, Salo Z, Li R, Wang M, and Graff JM: Adipose is a conserved dosage-sensitive antiobesity gene. Cell Metab 6: 195-207, 2007.

Seale P, Kajimura S, Yane W, Chin S, Rohas LM, Uldry M, Tavernier G, Langin D, and Spiegelman BM: Transcriptional control of brown fat determination by PRDM16. Cell Metab 6: 38-54, 2007.

Kim J-Y, van de Wall E, Laplante M, Azzara A, Trujillo ME, Hofmann SM, Schraw T, Durand JL, Li H, Li G, Jelicks LA, Mehler MF, Hui DY, Deshaies Y, Shulman GI, Schwartz GJ, and Scherer PE: Obesity-associated improvements in metabolic profile through expansion of adipose tissue. J Clin Invest 117: 2621-2637, 2007.

RESEARCH ON GASTRIC BYPASS SURGERY

Gastric Bypass Surgery Improves Longevity for the Severely Obese: Obesity places an individual at increased risk for type 2 diabetes, cancer, cardiovascular disease, and many other serious health problems. The popularity of diet books is evidence that, for many Americans, gaining weight seems to be very easy; however, losing those extra

pounds is difficult, and keeping them off can be a daunting task. Achieving and maintaining a healthier weight has not been an attainable goal for many who are morbidly obese. A procedure called gastric bypass surgery (a form of bariatric surgery) appears to be a successful solution for some of these individuals. Although gastric bypass surgery helps severely obese patients lose weight, it is an invasive surgery that involves risk. A recent NIDDK-supported research study, however, determined that gastric bypass surgery allows severely obese individuals the opportunity to enjoy longer, healthier lives.

The retrospective study to determine the long-term mortality after gastric bypass surgery was conducted with a cohort of 7,925 severely obese adult patients who had undergone gastric bypass surgery. Also participating in the study was a control cohort of 7,925 severely obese individuals who had not undergone gastric bypass surgery. Both groups were closely matched for age, sex, and body mass index. Scientists used the National Death Index to determine the death rates of members of both groups from all causes, as well as the death rates from specific causes. Notably, deaths by all causes were reduced 40 percent in the group who had surgery. When the numbers of deaths by specific causes were compared, it was found that in the surgery group, deaths caused by diabetes were reduced 92 percent, deaths from coronary artery disease were reduced by 56 percent, and deaths from cancer were decreased by 60 percent. Surprisingly, deaths that were not caused by disease, such as accidents and suicide, increased by 58 percent in the group who had undergone gastric bypass surgery. This increase in non-disease-related deaths warrants additional research.

This study provides much needed information for clinicians and patients considering gastric bypass surgery. Although gastric bypass surgery cannot be considered the optimal treatment for all obese patients, for some with extreme obesity it is currently the most effective treatment available. Previous studies have shown that quality of life improves for obese patients who undergo gastric bypass surgery. This study suggests that undergoing gastric bypass surgery may also decrease the risk of death from diabetes, cardiovascular disease, and cancer.

Adams TD, Gress RE, Smith SC, Halverson RC, Simper SC, Rosamond WD, LaMonte MJ, Stroup AM, and Hunt SC: Long-term mortality after gastric bypass surgery. N Engl J Med 357: 753-761, 2007.

New Metabolic Clinical Research Unit

On January 25, 2007, the NIDDK, in collaboration with the NIH Clinical Center, opened the new NIH Metabolic Clinical Research Unit (MCRU). Located in the NIH Clinical Center, the unit houses facilities that are permitting investigators to conduct cutting-edge research on the physiology, prevention, and treatment of obesity.

Obesity's "connection to co-morbid conditions like diabetes, heart disease and some forms of cancer will drive public health in the future," said NIH Director Dr. Elias Zerhouni, adding that the NIH Clinical Center is the ideal facility for multi-disciplinary research required to address the obesity epidemic.

A component of the *Strategic Plan for NIH Obesity Research*, the unit is designed to foster a collaborative research approach, bringing together experts from the fields of metabolism, endocrinology, nutrition, cardiovascular biology, gastroenterology, hepatology, genetics and the behavioral sciences.

"This is a unique facility that will house research protocols from several of the Institutes, making it the home of trans-NIH research at the Clinical Center," said Dr. Griffin Rodgers, NIDDK Director and co-chair of the NIH Obesity Research Task Force.

The metabolic unit includes 10 private inpatient rooms, a metabolic kitchen, an exercise room, special vending machines, and a communal dining area. The design of each room took into account the needs of the patient volunteers, with specially reinforced construction, amenities and equipment. The metabolic kitchen allows dietitians to control and analyze the composition of the patients' meals to calculate the exact nutrients consumed.

The unit's exercise equipment, physical activity monitors and body composition measurement tools are key resources for research protocols. The fitness equipment, including a treadmill and stationary upright and recumbent bikes, allows researchers to conduct stress and pulmonary function tests to observe the effects of exercise on weight loss.

To measure body composition, the unit provides access to a "Bod Pod®" and DXA scanner. The Pod measures total body density and lean and fat body mass using air displacement. The scanner sweeps the entire body with a small-dose X-ray to calculate how much of the body is made up of fat, muscle, and bone.

The signature feature of the metabolic unit is three "rapid response respiratory suites." These rooms allow researchers to measure volunteers' energy metabolism over 24 hours using non-invasive means. By analyzing air composition in the suite, researchers will be able to determine how much energy on a minute-to-minute basis a volunteer burns while sleeping, eating, or exercising and whether the energy comes from carbohydrate, protein, or fat. The metabolic suites also feature custom-designed vacuum-sealed portholes, or "isolette systems," through which measured food and other items can be passed and blood samples can be taken. These portholes also ensure that physiological measurements are not disrupted.

"People become obese or overweight because of small differences between calories taken in and calories expended over the long term," said Dr. Monica Skarulis, a senior clinical investigator with NIDDK's Clinical Endocrine Branch, who was integral to the planning of the metabolic suites. "These suites will allow clinical researchers to collect precise and accurate measurements necessary to test new and innovative hypotheses about energy metabolism."

The unit, which is available to all NIH Institutes and Centers for obesity research, opened with protocols sponsored by several Institutes including the NIDDK and the National Institute of Child Health and Human Development. The protocols will address how factors, such as a person's diet, level of exercise, or the amount of sleep he or she gets, combine with genetics to determine body weight. Dr. Skarulis said the unit seeks both obese and non-obese volunteers, "so everyone is welcome to consider enrolling."

For more information or to take a video tour of the new Metabolic Clinical Research Unit, please visit: *www2.niddk.nih.gov/Research/ClinicalResearch/MCRU/*

—Reprinted, in a slightly modified form, with permission from the NIH Record*; original article by Jenny Haliski published March 9, 2007.*

We Can!: *A National Program on Ways to Enhance Children's Activity & Nutrition*

To help address the growing problem of overweight in American children, the NIDDK is taking part in a national public education program called ***We Can!***, short for "Ways to Enhance Children's Activity & Nutrition." This program is a collaboration of the National Heart, Lung, and Blood Institute with the NIDDK, National Institute of Child Health and Human Development, and National Cancer Institute.

Overweight is a major public health concern in the United States that increasingly affects the nation's children and teens. Young people who are overweight are at greater risk for a lifetime of serious health problems, such as type 2 diabetes, high blood pressure, high blood cholesterol, heart disease, and asthma. The ***We Can!*** program was designed to help children ages 8-13 achieve and maintain a healthy weight, with support from their families and communities. Research-based program materials provide parents and caregivers with tips and activities to encourage three important behaviors to address childhood obesity:

- Improving food choices;
- Increasing physical activity; and
- Reducing time in front of the TV, video game, and computer screens.

We Can! is engaging with many professional, corporate, and community partners to reinforce its message.

As of December 2007, the ***We Can!*** program had grown from 14 intensive community sites to over 450 communities across 44 states since its launch in June 2005. The program also has a global reach, with sites located in Puerto Rico, Canada, Nigeria, the Northern Mariana Islands, and the Philippines. ***We Can!*** community sites include schools, parks and recreation departments, YMCAs, hospitals, health systems, universities, worksites, faith-based organizations, museums, and other settings. In April 2007, the NIH launched the ***We Can!*** City Program, with South Bend, Indiana; Gary, Indiana; and Roswell, Georgia becoming the first three cities to join the program. Since that time, other cities designated as ***We Can!*** Cities include Carson City, Nevada; Las Vegas; Boston; and Pittsburgh. In September, the first ***We Can!*** County joined the program representing Armstrong County, Pennsylvania.

These organizations, cities, and counties are conducting community-based programs and activities for parents/caregivers and children that engage multiple partners, including the media, in focusing on the need to prevent childhood obesity. City and county employees are also encouraged through ***We Can!*** programs and materials to maintain a healthy weight. The NIDDK Director, Dr. Griffin Rodgers, participated in launching a kick-off event in Roswell, Georgia, at which he presented Mayor Jere Wood with a road sign naming Roswell as an official ***We Can!*** City.

"The alarming trend of overweight in our children puts their health and well-being at risk," said Dr. Rodgers. "Roswell is serving as a model city by showing how communities can be a vital part of the solution."

Over 25 national partners and supporting organizations have joined this national effort. And, ***We Can!*** continues to grow by adding new partners, program materials, community sites, cities, and counties with the hope that, together, ***We Can!*** prevent childhood obesity.

More information about the ***We Can!*** program can be found at *http://wecan.nhlbi.nih.gov* or by calling 1-866-35-WeCan.

This road sign is posted in We Can! Cities around the country, such as Roswell, Georgia. The sign designates communities that are participating in efforts to help their children maintain a healthy weight.