



These fat cells were isolated using a method developed by Nobel laureate Dr. Martin Rodbell, whose prize-winning work was supported by NIDDK. Understanding fat cell biology is a key element in learning how to prevent and treat obesity. Photo: Dr. Joseph Brzostowski and Ms. Mary-Jane Zarnowski, NIDDK.

Obesity

Obesity is one of our nation's most pressing health problems, and it disproportionately affects racial and ethnic minorities—especially minority women. A strong risk factor for type 2 diabetes, obesity is also associated with other health conditions within the mission of the NIDDK, including, for example, gallbladder disease, urinary incontinence, and the fatty liver disease non-alcoholic steatohepatitis (NASH). Nearly 31 percent of adults in the U.S. are considered obese based on body mass index (BMI), a measure of weight relative to height.¹ Furthermore, 15 percent of children and teens in the U.S. are overweight, and are thus at risk for serious health problems early in life and as adults.²

The increase in prevalence of obesity in the U.S. in the past two decades is thought to result from the interaction of genetic susceptibility with behavior and factors in our environment that promote increased caloric intake and physical inactivity. The NIDDK has thus been supporting a multidimensional research portfolio on obesity ranging from basic studies to large clinical trials. This research includes, for example, investigations to elucidate the hormones and signaling pathways that influence appetite and energy expenditure; exploration of genetic factors that predispose individuals to obesity; studies of nutrition, including diet composition; research encompassing physical activity; and studies aimed toward obesity prevention through the development and testing of modifications of environmental factors in schools, the home, and other settings. A large clinical trial, Look AHEAD (Action for Health in Diabetes), will be examining the health effects of an intervention designed to achieve and maintain weight loss over the long term, primarily through exercise and decreased caloric intake, in obese individuals with type 2 diabetes. In another area of clinical research, a Bariatric Surgery Clinical Research Consortium has been established to facilitate and accelerate research on these surgical procedures, which are used to treat severe obesity. The NIDDK additionally supports research on eating disorders that are associated with obesity in some people. Highlights of recent advances from NIDDK-supported research on obesity are provided later in this chapter.

The NIDDK also sponsors education and information programs to bring the results of research to the public and health care providers. Through its Weight-Control Information Network (WIN), the NIDDK produces and distributes science-based information on obesity, weight control, nutrition, and physical activity to health professionals and consumers. The information includes fact sheets, educational brochures, and other publications. Another education effort is “Small Steps. Big Rewards. Prevent Type 2 Diabetes.” This educational campaign is promoting the dramatic effects of modest weight loss and moderate changes in diet and physical activity on reducing the risk for type 2 diabetes. The “Small Steps” campaign is based on the results of the Diabetes Prevention Program clinical trial, which was supported by the NIDDK and others. The campaign is sponsored by the National Diabetes Education Program (NDEP), a partnership of the NIDDK, the Centers for Disease Control and Prevention, and over 200 public and private organizations.

¹ This information is from data published at the time this document went to press; see, for example: Statistics Related to Overweight and Obesity. NIH Publication No. 03-4158, July 2003.

<http://www.niddk.nih.gov/health/nutrit/pubs/statobes.htm>. New statistical information is expected to become available in 2004.

² Because there is no generally accepted definition for obesity, as distinct from overweight, in children and adolescents, this document uses the terms overweight and obesity interchangeably for this age group.

ORGANIZATIONAL ENHANCEMENTS

New efforts are under way to accelerate progress in research to address the increasingly severe obesity epidemic and its serious implications for public health. Within the NIDDK, the Office of Obesity Research was created by the Institute Director in early FY 2003 to encourage multidisciplinary approaches to obesity and to coordinate obesity-related research within the Institute. The Office is located organizationally under the auspices of the Office of the Director, NIDDK, and its codirectors represent the two NIDDK Extramural Divisions with primary responsibility for obesity-related grants: the Division of Digestive Diseases and Nutrition and the Division of Diabetes, Endocrinology, and Metabolic Diseases. The NIDDK Director has also established an Obesity Research Working Group in the Institute. The responsibilities of this Working Group are to provide a forum for sharing and coordination of trans-NIDDK and trans-NIH obesity research activities; to assist the Director, NIDDK, in identifying research opportunities, initiatives, and advances; to identify and plan appropriate workshops and conferences; and to assist in preparation of obesity-related reports and responses to inquiries. An integral and essential component of the ongoing obesity research planning process is the solicitation of advice from external scientific and lay experts.

New Research Initiatives: Since its inception, the NIDDK Office of Obesity Research, with input from external experts, has developed new obesity-related initiatives and has planned several conferences on a variety of obesity-related topics. For example, one initiative will encourage studies on diet composition and energy balance to understand more fully how different attributes of foods (such as the amount and types of fats, carbohydrates, and proteins they contain) may affect appetite, weight loss, and other biological processes relevant to obesity. Another effort is soliciting grant applications for ancillary studies to existing obesity-related clinical trials and networks; such studies would help maximize the value of resource investments and contributions of volunteers. This effort is also one of several planned to

foster collaborations between basic scientists and clinical investigators. In another area, to enhance genetic research, the NIDDK is encouraging new studies in animals or other “model organisms” in which techniques for gene discovery are currently much more powerful than in humans. Identification of obesity-related genes in other organisms can lead scientists to discovery of similar obesity-related genes in humans. New multidisciplinary research collaborations will be promoted to bridge the gap between our understanding of behavioral influences on human obesity and our understanding, at the molecular and genetic levels, of biological pathways in the brain that are involved in food intake. Because of the critical importance—and extraordinary difficulty—of maintaining weight loss over the long term, the NIDDK is planning to solicit new studies to elucidate factors associated with weight maintenance and weight regain after intentional weight loss. The NIDDK is planning to solicit new research to help clarify the effects on overweight and obesity of environmental factors relevant to development, such as, for example, nutritional conditions present during fetal development. Another planned effort will promote research to identify biological markers associated with obesity-related health conditions using proteomics technology. Such studies seek to gain a comprehensive understanding of proteins in cells, tissues, and body fluids and how they function together.

Scientific Meetings—Setting the Stage for the Future: Examples of recent and upcoming meetings sponsored by the NIDDK to glean information and advice from external experts include the following. A workshop in the fall of 2003 fostered discussion of a variety of obesity-associated phenotypes (traits), aside from measurements of BMI, that might be useful to implement in a future large-scale human genetics study. The role of biological factors secreted by fat cells in the development of obesity-associated health conditions was the topic of another recent workshop. In early 2004, the NIDDK convened a conference on issues relating to “translating” the results of clinical trials on diabetes and obesity. One form of translational research aims to determine what can improve outcomes in diverse,

real-world populations and how to achieve these goals in a practical way that positively affects public health. An upcoming workshop will explore the role of lipids (such as different types of fatty acids, cholesterol, and other molecules) in the development of obesity and its associated diseases. All of these meetings will help inform the planning of future research efforts in obesity.

NIH OBESITY RESEARCH TASK FORCE

At the agency level, the NIDDK and the National Heart, Lung, and Blood Institute (NHLBI) are co-leading the NIH Obesity Research Task Force, which was established by the NIH Director in the Spring of 2003 to facilitate progress in obesity research across the agency. The Task Force is co-chaired by the NIDDK Director and the Acting Director of NHLBI, and its membership includes representatives from these Institutes and numerous other NIH components. Among the activities of the Task Force is the ongoing development of trans-NIH research initiatives for FY 2005 that would address pediatric obesity, neurobiologic research relating to obesity, and other areas. In response to a key element of the NIH Director's charge to the Task Force, an NIH strategic plan for obesity research is under development and is expected to be available in early 2004. To complement the strategic plan document, the Task Force is also preparing a website on NIH obesity research, also to be launched in early 2004. The primary purposes of this new website will be to help inform investigators of NIH funding opportunities for obesity research, to provide information on NIH-sponsored scientific meetings relevant to obesity, and to provide other information relevant to obesity research. In providing this information, the website will reflect the dynamic and ongoing planning process for obesity research at the NIH. Additionally, while the focus of this website will be research, the site will also include links to other NIH websites that provide information to the public and health professionals on weight loss, nutrition, physical activity, health problems associated with obesity, and other topics relevant to obesity.

Examples of Recent NIDDK-Supported Obesity Research Advances

BASIC RESEARCH

Basic research is providing insights into the molecular mechanisms underlying the development of obesity and its associated health conditions. The research advances highlighted below are examples of studies in animal models that are elucidating the roles of hormones and other molecules important in regulating body processes relevant to obesity.

Hunger Pangs in the Brain? A Potential New Brain Circuit for Appetite Regulation: Scientists have recently defined what may be a novel circuit in the brain for regulating appetite and energy balance. This circuit involves the appetite-stimulating hormone ghrelin. Levels of this hormone not only rise just before a meal to stimulate eating, but also rise after diet-induced weight loss—with a resulting increase in appetite. These effects provide one possible explanation for why dieters find it difficult to keep pounds off. Because ghrelin is made primarily in the stomach, and because there are “receptors” (docking sites) for ghrelin in the brain, this hormone was thought to be a signal from the gut to the brain to indicate when it was time to start a meal. While this gut-brain signaling may occur, ghrelin is also known to be manufactured within the brain itself. Taking this information as a potential clue that there may be another pathway for ghrelin's actions, a team of scientists has now further explored the brain's production of ghrelin. Many cells in the brain have been shown to be involved in energy balance. However, by studying the brains of rodents, the scientists discovered that ghrelin is made by a group of brain cells not previously known to influence energy balance. Intriguingly, these ghrelin-producing cells are located adjacent to brain cells that produce a protein called NPY, which functions to increase appetite—and which has also been known to help mediate the effects of ghrelin. The scientists also found that ghrelin can stimulate the activity of NPY-producing cells. Based on these results and several other experiments, the scientists

proposed that the brain's own indigenous source of ghrelin may activate the production of NPY by neighboring brain cells, thus leading to increased appetite. By uncovering what may be a previously unknown brain regulatory circuit, these studies provide further insights into the body's complex regulation of energy balance.

Animal Model To Study the Metabolic Syndrome:

Animal models of specific diseases or syndromes are critical tools to advance research. The metabolic syndrome is a cluster of medical problems, including obesity, insulin resistance, high blood pressure, and hyperlipidemia (high lipid levels), that appear in varying combinations, and that put people at increased risk for cardiovascular disease and for type 2 diabetes and its complications. Researchers have recently generated a mouse model that mimics the human metabolic syndrome. These mice were genetically-engineered to have fat cells that contained extra amounts of a cortisol-producing enzyme. The researchers had previously shown that the mice developed abdominal obesity and insulin resistance. They have now determined that the mice also have high blood pressure. This mouse model will be a useful tool to understand biological processes that are important in the metabolic syndrome. In addition, the cortisol-producing enzyme appears to play a role in regulating many aspects of the metabolic syndrome, including high blood pressure. Identifying agents that target this enzyme may be a useful approach for treating the metabolic syndrome.

Cowley MA, Smith RG, Diano S, Tschop M, Pronchuk N, Grove KL, Strasburger CJ, Bidlingmaier M, Esterman M, Heiman ML, Garcia-Segura LM, Nillni EA, Mendez P, Low MJ, Sotonyi P, Friedman JM, Liu H, Pinto S, Colmers WF, Cone RD, and Horvath TL: The distribution and mechanism of action of ghrelin in the CNS demonstrates a novel hypothalamic circuit regulating energy homeostasis. *Neuron* 37: 649-61, 2003.

Masuzaki H, Yamamoto H, Kenyon CJ, Elmquist JK, Morton NM, Paterson JM, Shinyama H, Sharp MG, Fleming S, Mullins JJ, Seckl JR, and Flier JS: Transgenic amplification of glucocorticoid action in adipose tissue causes high blood pressure in mice. *J Clin Invest* 112: 83-90, 2003.

OBESITY, DIET AND ACTIVITY—EXAMPLES OF STUDIES WITH ADULT VOLUNTEERS

Obesity results from an energy imbalance—that is, when the number of calories eaten exceeds the number of calories burned for energy in order to maintain essential body functioning and to power physical activities such as walking. Thus, investigators are conducting research on behavioral changes in diet and activity that may help people to lose excess weight or prevent weight gain. A number of studies are exploring various types of dietary modifications and how they may affect health and body weight. With respect to physical activity, researchers are addressing both the problems associated with too much sedentary behavior and the potential benefits of increasing activity.

Low Carbs versus Low Fat—Is Either Diet Better?:

Investigators recently compared the effects of a specific low-carbohydrate diet with a more conventional diet in a small-scale study of obese men and women. The test diet was low in carbohydrates and high in fat and protein; the “conventional” diet was high in carbohydrates and low in fat and calories. Participants in the study were assigned to follow one of these two diets for a year. While the participants on the low-carbohydrate diet lost more weight early on than those on the conventional diet, by the end of the year there was no significant difference in weight loss between the two groups. With respect to several health conditions associated with obesity, participants on the low-carbohydrate diet had a greater improvement in some risk factors for heart disease, including a greater increase in high-density lipoprotein cholesterol (“good” cholesterol) and a greater decrease in triglyceride concentration. As is often the case with diets, however, many participants from each group did not adhere to their assigned diet and dropped out of the study before the end of the year. Overall, the researchers concluded that longer and larger studies would be necessary to adequately assess whether low-carbohydrate, high-protein, high-fat diets are safe and effective.

Increased Risk for Obesity and Type 2 Diabetes From TV Watching and Other Sedentary Behaviors:

In a large study of thousands of women, researchers found that sedentary behaviors—and especially sitting while watching television—are predictive of significantly greater risk of obesity and type 2 diabetes. Those who, on average, watched more TV per day were at higher risk. In fact, each 2 hour per day increase in TV watching during the course of the study was associated with a 23 percent increase in risk for obesity, and a 14 percent increase in risk for developing type 2 diabetes. This research adds to earlier findings that related TV watching and obesity in children.

Exercise and Weight Management: In a new study, investigators observed beneficial effects of moderate intensity exercise on weight management in young men and women who previously had sedentary lifestyles and were overweight or moderately obese. Because the participants did not change their diets during the study, the results highlight specific effects of exercise on weight. Participants were assigned to either to a supervised 16-month exercise program or to a control group instructed to maintain their usual activity levels. The exercise program consisted mainly of walking on treadmills, and the participants started with an initial 20 minutes and built up to 45 minutes per session, five sessions a week. Their goal was to burn a minimum of 400 calories per session. The men in the study lost an average of approximately 6 percent of their body weight, and most of this weight loss came from body fat. Weight losses of similar amounts have been shown previously to have positive effects on health. Visceral fat—that is, fat surrounding the internal organs in the abdomen—declined significantly in the men who exercised; this result is encouraging because visceral fat is thought to be particularly associated with health risks. The results of the exercise program were different in women, although still beneficial. The female participants did not lose weight, but they also did not gain weight. By contrast, the women in the sedentary control group gained extra weight by the end of the study period. The women who exercised also had slightly less total body fat and visceral fat as compared to the

women in the control group. The reasons for the differences seen between the men and women are as yet unclear, and it may be that diet modification to reduce energy intake, in addition to this level of exercise, would be needed to achieve weight loss in women. In considering the positive effects of the study, the investigators pointed out that the challenge now is to develop effective ways to help overweight and moderately obese people maintain an exercise program over the long-term.

Donnelly JE, Hill JO, Jacobsen DJ, Potteiger J, Sullivan DK, Johnson SL, Heelan K, Hise M, Fennessey PV, Sonko B, Sharp T, Jakicic JM, Blair SN, Tran ZV, Mayo M, Gibson C, and Washburn RA: Effects of a 16-month randomized controlled exercise trial on body weight and composition in young, overweight men and women: The Midwest Exercise Trial. *Arch Intern Med* 163: 1343-50, 2003.

Foster GD, Wyatt HR, Hill JO, McGuckin BG, Brill C, Mohammed BS, Szapary PO, Rader DJ, Edman JS, and Klein S: A randomized trial of a low-carbohydrate diet for obesity. *N Engl J Med* 348: 2082-90, 2003.

Hu FB, Li TY, Colditz GA, Willett WC, and Manson JE: Television watching and other sedentary behaviors in relation to risk of obesity and type 2 diabetes mellitus in women. *JAMA* 289: 1785-91, 2003.

OBESITY IN CHILDREN AND ADOLESCENTS

The dramatic increase in overweight and obesity in children and adolescents has ominous implications for our Nation's future health. There is an ominous link between obesity and such serious diseases as type 2 diabetes—once viewed as a disease of older adults but now increasingly seen in children. Thus, the rise in childhood obesity may portend a lifetime of devastating health problems for many of our country's children and adolescents, as well as an escalation in the demands on our health care system. Following is one example of recent NIDDK-supported research on adolescent obesity.

Effect of Diet Macronutrient Content on Weight Loss

in Obese Adolescents: As noted, type 2 diabetes is increasingly being diagnosed in young people. Most youth with this form of diabetes are obese, and it is therefore imperative to design interventions to prevent obesity, or to promote weight loss in adolescents who are already obese. In order to understand the role of diet macronutrient content in weight loss in obese adolescents, researchers have compared a conventional, low-fat diet with an experimental diet that has a reduced glycemic-load (GL). GL is based on another parameter, called the “glycemic index,” which is a measurement of how a food changes blood glucose levels in a short period of time. The researchers found that obese adolescents who ate a low-GL diet lost more weight compared to those on a conventional diet. This was an especially interesting result, because the adolescents on the low-GL diet were allowed to eat until they reached satiety, whereas those in the low-fat diet group maintained a certain number of calories. Another benefit from the low-GL diet was that it reduced the progressive rise in insulin resistance seen during the study more than the low-fat diet. Because this was a small study of 14 adolescents, further studies will have to be performed to determine if a low-GL diet has the same benefit in a larger group. If so, this may be a potential intervention strategy to promote weight loss and improve insulin sensitivity in obese adolescents.

Ebbeling CB, Leidig MM, Sinclair KB, Hangen JP, and Ludwig DS: A reduced-glycemic load diet in the treatment of adolescent obesity. *Arch Pediatr Adolesc Med* 157: 773-9, 2003.

OBESITY-ENVIRONMENTAL INFLUENCES AND LONG-TERM HEALTH EFFECTS

Years of Life Lost Due to Obesity: As one way to address the seriousness of the obesity epidemic, a variety of public health messages can be developed to convey the deleterious health effects of obesity. Thus, to build upon existing information available for health campaigns, a group of scientists recently sought to express the impact of obesity on individual

health in terms of “years of life lost.” This approach assesses the difference between the expected life span of an individual who is not obese (or overweight) and the number of years the person might live if he or she were obese. To determine the “years of life lost” due to obesity, the scientists evaluated data on Caucasian and African American men and women from the third National Health and Nutrition Examination Survey (NHANES III), which collects information on the health and diet of people in the U.S. The scientists found that the “years of life” lost associated with obesity was most dramatic at younger ages. Caucasian men 20 to 30 years old who are severely obese can expect lifespans up to 13 years shorter than someone who is not overweight; severely obese Caucasian women may lose up to 8 years of life. Among young African-American women, those who are severely obese may lose up to 5 years from their expected remaining life span. Alarming, severely obese young African-American men may lose up to 20 years of life. While the reasons for the race and gender differences are not yet clear, the study presents a striking picture of the effects of obesity. The scientists further placed their findings in the context of yet another harmful aspect of obesity: not only does obesity shorten life, but previous research suggests that it also impairs the quality of life.

A Few Less Bites and a Few Extra Steps—Dealing with Obesity in Our Current Environment:

Given the dramatic increases in levels of obesity in the population, a team of researchers recently proposed a short-term strategy that may help individuals prevent further weight gain in our current “obesogenic” environment. Their strategy consists of small behavior changes that would hopefully fit into most people’s lifestyles: eating “a few less bites” at each meal, even without changing the types of foods eaten, or walking an extra mile—amounting to 15 to 20 minutes per day—even if the extra walking is not done all at once. Essentially, these changes would be designed to shift energy balance by 100 kilocalories per day, through reducing calorie intake and/or increasing calorie burning through physical activity. How did the researchers end up

with this number of calories? By reviewing data from large-scale national studies, they first estimated the average weight gain per year of adults in the U.S. Then, estimating the number of calories needed to form each extra pound of body weight, the researchers calculated an “energy gap” of 100 kilocalories—the amount of energy that people who are gaining weight may be taking in and storing as excess pounds, rather than burning off. The strategy of small behavior changes to close this energy gap has yet to be tested with volunteers, and it is not clear how it may need to be adjusted to prevent excess weight gain in children. Nevertheless, the researchers suggest that their strategy, with a specific target of preventing even further weight gain—rather than attempting to reduce current levels of obesity—may be something feasible that can be pursued now to halt the rising obesity epidemic.

In addition to their short-term strategy, these researchers also advocate longer-term and more challenging goals. These include: (1) promoting broad social changes to build an environment more conducive to healthy lifestyles, and (2) developing improved ways to help people change behaviors in an environment that may never revert to a time when a lesser food supply and a greater need for physical labor might have made worries about body weight unnecessary.

Fontaine KR, Redden DT, Wang C, Westfall AO, and Allison DB: Years of life lost due to obesity. *JAMA* 289: 187-93, 2003.

Hill JO, Wyatt HR, Reed GW, and Peters JC: Obesity and the environment: Where do we go from here? *Science* 299: 853-5, 2003.

WIN: The Weight-Control Information Network

When the Department of Health and Human Services (HHS) released its report entitled, “The Surgeon General’s Call to Action to Prevent and Decrease Overweight and Obesity,” Secretary Tommy G. Thompson warned that, “Overweight and obesity are among the most pressing new health challenges we face today.” It has been estimated that 300,000 deaths each year in the U.S. are associated with obesity and overweight, and the numbers are increasing. Obesity is an epidemic that must be brought under control. The WIN is an NIDDK health information service directed at helping to reach this goal.

Established in 1994, the NIDDK’s Weight-control Information Network (WIN) is a national information service that produces and provides science-based information on obesity, physical activity, weight control, and nutrition to health professionals, people who are overweight or obese, and other information consumers. The WIN has reached out to all age groups and diverse ethnic and racial groups with its materials.

Recently, the WIN published a series of booklets, “Healthy Eating and Physical Activity Across Your Lifespan,” to encourage better eating and physical activity habits. The series contains four booklets entitled, “Tips for Parents,” “Tips for Adults,” “Tips for Older Adults,” and “Tips for Pregnant Women.” These booklets are published in both English and Spanish language versions. The latest publication produced by the WIN is “Just Enough for You.” This publication defines the difference between food portions and food servings, and provides information on ways to control the size of food portions and to improve nutrition with minimal changes in eating habits.

Non-Hispanic African-American women have been hardest hit by the nation-wide rise in overweight and obesity. Based on body mass index (BMI)—a measure of weight relative to height—77.3 percent of adults in this group are overweight or obese. The WIN’s “Sisters Together: Move More, Eat Better” initiative was developed in the 1990s to encourage African-American women 18 years of age or older to maintain a healthy weight by increasing physical activity and eating more healthful food. A planning guide and kit based on the pilot phase of this initiative are available to provide step-by-step instructions for planning, promoting, implementing, and evaluating community health awareness programs to prevent African-American women from becoming overweight. “Sisters Together” has also produced other informational brochures.

The WIN is also coordinating with the Institute’s Look AHEAD (Action for Health in Diabetes) clinical trial. The Look AHEAD trial is a large-scale, multi-center trial that is examining whether a lifestyle intervention designed to achieve voluntary long-term weight loss will improve cardiovascular and other outcomes over the long term in obese individuals with type 2 diabetes. The WIN is providing a portion of the information on physical activity and healthy eating that is given to trial participants.