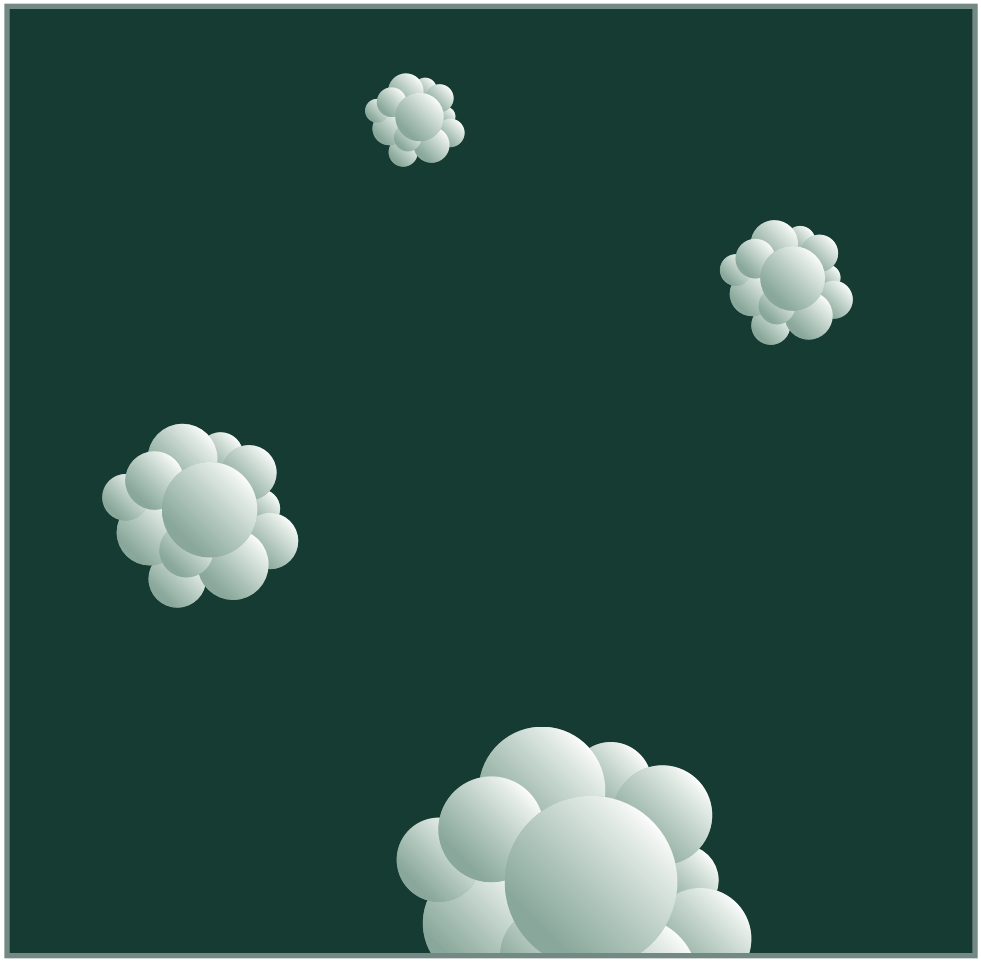


Fat cells are no longer considered passive storehouses for excess energy. Instead, we now know that fat cells actively communicate with the brain and other tissues by making and secreting special hormones, or signaling proteins, which regulate appetite and metabolism. This new knowledge provides targets for the development of new pharmacological approaches to treating obesity and insulin resistance. Graphic: the Hill Group.

Extraordinary Opportunity:

Obesity — Critical in Diabetes and a Major Problem of its Own

Obesity is one of the fastest growing health problems in the U.S. It is estimated that 60 percent of the adult population is overweight or obese. In the last two decades, the prevalence of obesity has nearly doubled, increasing from 15 to 27 percent of the American adult population. Obesity is also on the rise in children and adolescents; 13 percent of America's youth are now overweight, with ominous implications for our nation's future health. Obesity is associated with a number of diseases, such as cardiovascular disease and stroke, as well as type 2 diabetes. Approximately 80 percent of the type 2 diabetes in the U.S. occurs in overweight or obese individuals. Even modest reductions in weight can have remarkable effects on improving blood glucose levels and preventing diabetes. As demonstrated recently by the landmark Diabetes Prevention Program (DPP), a five to seven percent sustained reduction in weight can delay or prevent the onset of diabetes in a high risk population.

The DRWG recognized the critical role of obesity in the pathogenesis of diabetes and the extraordinary opportunities stimulated by the discovery of leptin and the completion of the human genome project. Recent scientific discoveries regarding the biological mechanisms controlling food intake and energy expenditure create a new terrain for the development of new families of drugs, which may combat weight gain or control its deleterious effects. Galvanized by advances in technology, as well as by increased recognition of obesity's public health importance, researchers are uncovering the links between obesity and insulin resistance as well as the fundamental pathobiology leading to the progression to frank diabetes. Major initiatives to discover the genetic basis of obesity have also begun to uncover genes that may determine susceptibility not only to obesity but also to the subsequent development of diabetes. Genes have been implicated in control of food preference and other obesity-associated behaviors.

The DRWG emphasized the importance of environmental and social factors in the rapid rise in the numbers of overweight and obese adults and children. Both an increase in caloric intake and a trend toward sedentary lifestyle have been implicated in the rise in obesity. Improved understanding of the environmental factors, which are in large part responsible for the obesity epidemic, together with behavioral research on how to modify risk in today's environment, have the potential to reduce the incidence and morbidity of obesity-related diabetes. Although preventing weight gain and sustaining weight loss are difficult, promising early results of new treatment strategies suggest these goals can be achieved. The DRWG Strategic Plan recognized the need for additional research on the social and biological factors influencing lifestyle and, particularly, the need to develop behavioral intervention strategies that can reduce the incidence and severity of obesity, especially in high risk populations.

Since the publication of the DRWG report, significant advances have been made in our understanding of the causes of obesity and its link to diabetes. Behavioral interventions have been developed based on an increasing knowledge about the role of exercise and diet in obesity. Recently, the NIH has initiated or expanded multiple programs to stem the rising incidence of obesity. Notable new initiatives have focused on:

- Expanding research on the biological basis of obesity and its role in diabetes and cardiovascular disease;
- Studying special populations — such as those with genetic and HIV-related fat dystrophy — to understand the link between obesity, insulin resistance, and diabetes and to explore treatment strategies;
- Encouraging the development of new understandings from behavioral research and their application to the prevention and treatment of obesity;
- Developing innovative approaches — such as school-based behavioral intervention trials — to prevent obesity in target populations;
- Exploring environmental changes to prevent inappropriate weight gain;
- Initiating a major clinical trial, Look AHEAD, to ascertain the long-term consequences of weight loss in people with type 2 diabetes;
- Studying the use of bariatric surgery in the treatment of morbid obesity and exploring the mechanisms by which this impacts obesity and diabetes; and
- Translating research advances into practice, and developing education programs to encourage healthy lifestyles.

Understanding the Link Between Obesity and Diabetes

While the link between obesity and insulin resistance is clear, it is not straightforward. Multiple genetic, environmental, and hormonal factors are implicated in the progression from insulin resistance to diabetes. Furthermore, insulin resistance is observed in both lean and obese individuals.

Many obese individuals with insulin resistance never progress to diabetes. In some populations, such as Asian Americans, the degree of obesity associated with an increased risk of diabetes is much lower than in other racial and ethnic groups. Numerous studies support a role for insulin resistance as a risk factor for cardiovascular disease, distinct from either obesity or diabetes. Recent work demonstrates a role for intracellular lipid accumulation in muscle, liver, and endocrine pancreas in the development of insulin resistance in those tissues. Concurrent work with animal models (reviewed in the section on "Cell Signaling and Cell Regulation") has defined roles for insulin resistance in each of these tissues in the constellation of features that comprise diabetes. The exciting discoveries about basic mechanisms of energy regulation—together with the increasing sophistication of technologies and animal models—should now permit researchers to tackle the more difficult, but perhaps more realistic, situation in which diet and exercise level can be added as variables. This should provide an important bridge between powerful animal models and human disease.

EXERCISE AND INSULIN RESISTANCE

Recent studies in both humans and animal models have shown a direct effect of exercise to reduce muscle insulin resistance in both acute and long-term settings. A clear correlation exists between load-bearing exercise and improvement in insulin sensitivity in humans, while the effect of aerobic exercise is less straightforward. The use of animal models to study the relationship of exercise and insulin resistance should enable investigators to identify specific mediators of exercise-induced reductions in peripheral insulin resistance. While the linkage between adiposity (stored body fat) and insulin resistance is well substantiated, additional studies are needed to establish interactions between exercise and adiposity. The effect of exercise in increasing energy expenditure is well recognized, but recent studies suggest more complex effects of exercise on stored body fat. A more comprehensive understanding of nutrient partitioning, hormonal factors and physiological effects of exercise will be required to obtain definitive information on these interactions.

CENTRAL VERSUS PERIPHERAL OBESITY

Concurrent with the revelation that adipose tissue is more than a storage site for fat and, in fact, plays a critical role as an endocrine organ, is the appreciation that fat deposited in varying regions of the body may be metabolically distinct. Recent data suggest that abdominal fat, and particularly the visceral fat associated with the abdominal organs, may be associated with the deleterious effects of obesity. While serum levels of TNF-alpha, a cytokine that has been demonstrated to cause insulin resistance in animal models, have been associated with extent of obesity in some studies, others have failed to show a correlation. A recent study has shown, however, that tissue levels of TNF-alpha from visceral fat correlate with both obesity and insulin resistance, providing support for a role for this factor in human obesity.

Another line of evidence suggests that visceral fat may contribute to obesity and insulin resistance through release of particular steroid hormones, the glucocorticoids. While increased levels of serum glucocorticoids in patients with Cushing Syndrome are associated with obesity, elevated glucocorticoids in peripheral serum are generally not observed in obese individuals. Recent animal model data suggest a potentially important local role for glucocorticoids in visceral adipose tissue. A genetic manipulation that increased production of these hormones in fat tissue led to visceral obesity and insulin resistance. These changes might be due to a local effect of the increased glucocorticoid hormone levels within the abdominal fat tissue or to effects of glucocorticoids on the liver, given that the portal circulation feeds into the liver from the abdominal organs. These new data reopen the debate on the potential role of glucocorticoids in obesity.

INSIGHTS FROM FAT REDISTRIBUTION IN HIV DISEASE

Lipodystrophy is characterized by selective loss of fat from various parts of the body. In progressive lipodystrophy, there is increased deposition of fat (lipohypertrophy) in the abdomen and trunk, and/or loss of fat (lipoatrophy) in the face and extremities. It appears to occur commonly in HIV patients on Highly Active Anti-Retroviral Therapy (HAART). HAART has also been increasingly associated with hyperinsulinemia and pre-diabetes; to date, frank diabetes has been reported less frequently. However, concern about eventual progression to diabetes is real, particularly in those patients who also have accumulation of abdominal, particularly visceral, fat. Patients receiving HAART may also have altered lipid profiles, including the hypertriglyceridemia and low HDL cholesterol levels characteristic of diabetes. In non-HIV-infected individuals, coexistence of these lipid alterations and insulin resistance confers additive risk for the development of atherosclerotic heart disease, making these HAART-associated side effects a serious potential public health concern. In addition to concerns over potential long-term health implications of these changes, distress over the often disfiguring changes in body fat distribution has caused some patients to stop taking antiviral medications. Although the incidence of diabetes in the HIV-infected population has not been alarming to date, the marked hyperinsulinemia seen in this patient population, along with enrichment for other risk factors for diabetes and cardiovascular disease such as drug abuse, does suggest that further investigation of the basis for the metabolic syndrome associated with HIV and its therapy may uncover links between visceral obesity and insulin resistance, with important implications for understanding the link between obesity and type 2 diabetes.

INSIGHTS FROM GENETIC LIPODYSTROPHY SYNDROMES

A deficiency of fat cells is central to a number of genetic lipodystrophy syndromes in which patients have severe insulin resistance, diabetes, and other metabolic abnormalities (reviewed in "Genetics"). Patients with these disorders have made important contributions to our understanding of fat as a metabolic organ and its role in insulin resistance. Now research has also yielded a major new therapy for this population. Treatment with leptin, a hormone normally produced by fat cells, dramatically improved control of diabetes and lipid profiles in these patients. These results suggest that leptin may provide a signal that regulates sensitivity to insulin in the whole body. Recently, the gene responsible for one of these rare syndromes was identified and its function is under investigation. Further studies of the mechanisms involved in these unusual obesity-related syndromes will help to clarify the link between obesity, insulin resistance, and progression to diabetes.

Behavioral and Environmental Interventions to Reduce Obesity

Although genetic factors are believed to contribute substantially to the predisposition towards obesity, the dramatic increase in obesity prevalence over the past two decades is a consequence of environmental factors interacting with genetic susceptibility.

Increased food supply and decreased physical activity favor increased energy intake along with decreased energy expenditure. While genetic factors may account for a significant proportion of variability in body weight within a population, it has been suggested that environmental factors account for most variability in body weight between populations or over time. While molecular and genetic research will undoubtedly provide important insights into the control of body weight, which may eventually lead to improved efforts in prevention and treatment, it is unlikely that such approaches alone will overcome the substantial environmental pressures for over-consumption and sedentary behavior currently affecting Americans. Environmental change has been key to the development of the new epidemic of obesity and environmental and behavioral changes are pivotal to its reversal.

CHANGES IN EATING PATTERNS CONTRIBUTE TO INCREASING OBESITY

Environmental factors believed to play a role in the development of obesity include those that increase energy intake, such as larger portion sizes, greater frequency of restaurant meals, and the use of more fast foods and convenience foods. The role of nutrition is complex. While societal changes in eating patterns and food availability have undoubtedly contributed to increased obesity, diet selection is a composite of many factors—social, behavioral, and genetic. Food preference involves physiological as well as conscious mechanisms. Studies in twins have also shown a genetic contribution to food preferences. Several recent studies have shown that breastfeeding is associated with a lower BMI later in life. Exploring whether this effect is due to a difference in nutritional status during development or is manifested through other pathways, possibly even food preference, will require both clever and thorough follow-up studies.

IMPORTANCE OF PHYSICAL ACTIVITY UNDERSCORED

Numerous environmental factors also lead to decreased energy expenditure. Work is more likely to be sedentary than in the past, with near universal use of automated equipment and electronic communications. At home, wireless phones, remote controls, and various labor saving devices also decrease physical activity. More time is spent on the computer, watching television, and playing videogames—particularly among children and adolescents. At the same time, the number of schools requiring daily physical education has declined. Suburban communities often lack sidewalks, and this makes it difficult to walk even short distances to stores and recreation. Many individuals report difficulties going out to exercise because their neighborhoods are perceived as unsafe. In addition, children often lack facilities to engage in active play. The importance of physical activity is underscored by a recent study demonstrating a strong correlation between participation—or lack thereof—in youth sports and subsequent adult activity level, as well as obesity.

EMERGING SUCCESSES WITH BEHAVIORAL AND ENVIRONMENTAL INTERVENTIONS

Sustained weight loss in obese individuals has been remarkably difficult to achieve. The multitude of weight loss regimens and special diets marketed to overweight individuals is a testament to the inability of these programs to help significant numbers of people lose weight and maintain their new body weight for periods beyond a few months. The exceptional successes that have been reported in the literature—including the recent results from the DPP—have required intensive and prolonged behavioral intervention by teams of nutritionists, exercise physiologists, and physicians. New research is building on these results and attempting to develop less costly approaches that can be provided in group settings. Recently, a number of small pilot studies have published encouraging results using very creative approaches to increase activity and improve dietary habits in specifically targeted populations. One such study was able to achieve significant reductions in BMI among school children who participated in a program to reduce time watching television and playing video games. A second study, Planet Health, was able to replicate this effect in girls, but not boys.

EXPANDING BEHAVIORAL RESEARCH

Since the DRWG Strategic Plan was issued, the NIH has solicited and funded a number of pilot studies to explore innovative approaches to preventing obesity in minorities and other populations at increased risk. A recent conference brought the investigators conducting these studies together to share results and to consider how to build on these efforts. Studies are comparing approaches focused on physical activity and caloric restriction as well as how these approaches interact. Research is being encouraged to explore the role of depression, anxiety disorders, and other mental health problems on the development and therapy of obesity. The NIH will also fund a number of community-based studies to test environmental interventions to prevent obesity. These studies will employ a wide range of strategies to improve dietary habits and/or increase activity. Direct and active collaboration with members of the community is an essential foundation of this initiative to ensure that culturally sensitive programs are designed that incorporate health practices within the study population. Particularly encouraged are partnerships with community organizations — such as schools, supermarkets, restaurants, churches, and workplaces — so that successful interventions can be translated into larger-scale efforts.

Surgical Approaches to Treatment of Obesity

The number of individuals with severe obesity is increasing at an alarming rate. These individuals are at much greater risk for increased morbidity and mortality, and behavioral interventions are particularly challenging in this group.

Surgical intervention in this population has been successful in the long-term maintenance of weight loss and the subsequent reduction in co-morbid conditions such as diabetes. Potential complications associated with bariatric surgery, along with cost and lifestyle factors, have limited the application of this procedure to a broader patient population. However, improved methods, including the ability to perform this surgery laparoscopically, hold promise of increasing its utility in the management of severe obesity.

Physicians generally have used two approaches to the surgical treatment of obesity. The size of the stomach can be reduced with staples or the length of the intestine can be reduced by resection. These alterations can impact multiple pathways involved in the regulation of body weight. Incretins and other hormonal signals may be altered by reducing the amount of gastrointestinal tissue that secretes these factors, or by decreasing the volume of food

continued

required to stimulate release of satiety factors. The total mass of nutrient uptake may be reduced as well. Exploration of questions related to the mechanisms underlying the effects of bariatric surgery have been hindered by a lack of standard surgical procedures and of quantitation of changes in gastrointestinal surface area as a result of surgery. Results from a number of studies suggest that the effects of bariatric surgery are complex. For example, within hours post-surgery there are marked improvements in insulin sensitivity and even restoration of euglycemia in some patients with diabetes. Careful investigation into the endocrine and metabolic changes that result from bariatric surgery may provide valuable clues to the link between diabetes and obesity.

To pursue these questions, the NIH will establish a consortium of bariatric surgery centers to collect systematic outcome data for this treatment paradigm in a standardized and controlled setting and to define the endocrine, metabolic, and behavioral changes associated with this procedure. This consortium will provide a new resource to help elucidate the mechanisms by which these changes are evoked, and may provide a unique window into the biological links between diabetes, cardiovascular disease and obesity.

Translation and Education Efforts to Reduce Obesity

In many cases, overweight and obesity, along with the associated risk of type 2 diabetes, are preventable. However, recent studies show that half of Americans are not regularly physically active, and the strategies that Americans use for weight loss are not successful.

Since the NIH issued its "Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: Evidence Report" in 1998, this material has been translated into a series of formats for use by health care providers and public education efforts have intensified. The NIH's Weight Control Information Network (WIN)—which provides health professionals and consumers with science-based information on obesity, weight control, and nutrition—is one part of a larger network of NIH supported education efforts directed toward public awareness of the hazards of obesity and how it can be prevented and treated. The NIH has also collaborated with the CDC and other agencies in public outreach efforts. For example, Hearts N' Parks is an innovative, national, community-based program supported by the NIH and the National Recreation and Park Association, focused on increasing physical activity through use of public recreational facilities.

Educational outreach must go beyond programs directed at the public. A recent study found that only 43 percent of obese people who had a routine check up in the past year were advised by a health professional to lose weight. Other recent studies have shown that physician nutrition and diet habits are related to the extent and frequency of patient counseling on healthy lifestyle. Thus, efforts to introduce a healthy lifestyle to health providers may

well have an amplified effect in their involvement in obesity treatment and prevention efforts, and in patient compliance. As effective new tools for behavioral intervention are developed through research, it will be essential to bring these rapidly to the clinic, where they can be deployed.

Education and translation efforts must also be specifically designed and targeted to high risk populations. For example, African American women are at particularly high risk for obesity and diabetes. In-home surveys in an inner city African American community illustrate the need for effective methods to disseminate health information and deliver behavioral intervention programs in the community setting. In this study population, which had a high prevalence of obesity, only 61 percent of obese individuals were trying to lose weight, and importantly, only 35 percent of those trying to lose weight were using recommended approaches. Since the DRWG's recommendations were issued, the NIH has developed a new program in association with WIN. This program, "Sisters Together: Move More, Eat Better," involves use of the media to encourage African American women to maintain a healthy weight through physical activity and healthy eating habits.

Important Questions Remain to be Answered

Successful prevention and/or treatment of obesity would have a major positive impact on the incidence and severity of diabetes and its complications.

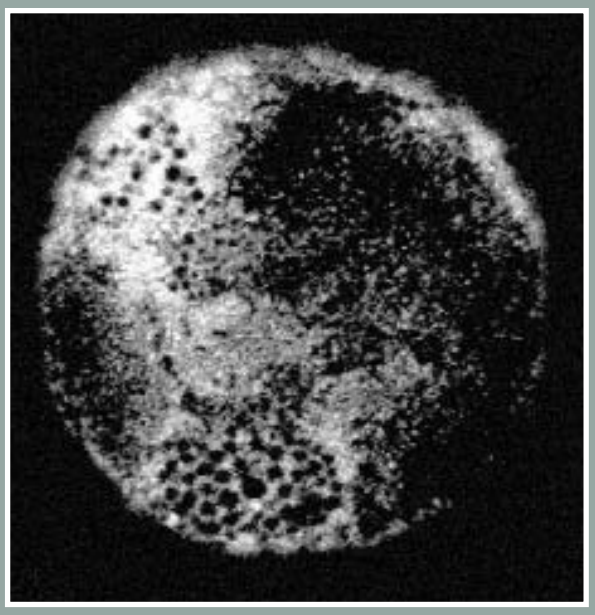
The DPP has now demonstrated the efficacy of weight loss in preventing diabetes in a diverse American population and numerous other studies have shown weight loss mitigates risk factors for diabetes and cardiovascular disease. A major challenge is the extrapolation of behavioral and environmental approaches for healthy eating and physical activity to the large numbers of overweight individuals at risk to develop diabetes and to those at risk for overweight and obesity. Expanded efforts are needed to identify markers for risk of obesity and associated adverse outcomes such as diabetes.

The magnitude of the problem of obesity and its human and economic toll drive us to apply all the new tools at our disposal to its solution. This will involve a major commitment to developing cost-effective behavioral approaches to prevention and therapy. In addition, new molecular and genetics tools — such as haplotype maps, genomic and proteomic approaches, new computational methods, and new approaches to metabolic and physiologic characterization — will help unravel the web of genetic and environmental interactions underlying the current epidemic of obesity. These approaches may help us explain food preference, energy expenditure and response to intervention; identify potential therapeutic targets; and point the way to new methods of prevention and therapy.

Story of Discovery

The Ominous Link Between Obesity and Type 2 Diabetes

Americans are facing an epidemic of obesity and type 2 diabetes, according to epidemiologic studies. Type 2 diabetes, a devastating illness responsible for 90 to 95 percent of the 17 million people who have diabetes, can lead to serious complications including blindness, kidney failure, lower limb amputations, and heart disease. Although genetic factors may predispose a person to be overweight or develop diabetes, other factors must also be involved, because our genes could not possibly have changed quickly enough to account for the rapid increase in the prevalence of obesity and type 2 diabetes. Research indicates that the obesity problem essentially results from Americans' eating too much and exercising too little. But how is an increase in obesity related to an increase in diabetes? For a long time, scientists have known that obese or overweight people are far more likely to develop type 2 diabetes; in fact, 80 percent of patients with type 2 diabetes are overweight or obese. However, only recently have scientists begun to find the biological molecules that connect these two health problems.



A fat cell is labeled to show the distribution of leptin—the product of an important obesity gene discovered through fundamental research. Leptin plays a key role in sensing energy stores and regulating appetite and metabolism. Researchers are striving to understand the hormone's role in the processes that underlie obesity and insulin resistance. Photo: Dr. Daniela Malide and Dr. Samuel W. Cushman, NIDDK.

Type 2 diabetes develops through a multi-stage process. First, the body becomes unable to use insulin effectively, a condition known as insulin resistance. Insulin is a protein hormone made by cells in the pancreas called beta cells. Insulin normally helps the body maintain a healthy level of glucose (sugar) in the blood by causing fat and muscle cells to store glucose and by reducing glucose production in liver cells. When insulin resistance develops, the beta cells try to compensate by making more insulin. For a while, this helps keep blood glucose levels relatively normal, but eventually the beta cells become exhausted and cannot produce enough insulin to overcome the insulin resistance. At this point, individuals develop a condition called "pre-diabetes," in which blood glucose levels are higher than normal but not as high as those in diabetes. Left untreated, however, this condition frequently progresses to full-blown type 2 diabetes. Unfortunately, people with insulin resistance and pre-diabetes experience no outward symptoms and thus are unaware of this silent progression towards diabetes.

How is obesity connected to insulin resistance and diabetes? Clues are being found in unexpected places. Surprisingly, fat cells are not passive storehouses for fat, just keeping fat in case it is needed for energy. Instead, fat cells actively sense changes in energy availability and signal the brain and other tissues to regulate feeding and cellular processes. Scientists are learning that fat cells send out these signals in the form of special hormones, or signaling proteins, which the fat cells make and secrete. With the discoveries of novel signaling hormones, scientists are learning that the connection between fat and diabetes involves a complex balance of fat cell hormones.

Among the signaling proteins made by fat cells are leptin, resistin, and adiponectin (also known as Acrp30). After a meal, fat cells release leptin. This hormone signals the appetite control center in the brain to stop eating. Scientists found that mice lacking the gene for leptin overeat and become obese. When given leptin, these mice lose weight. Unfortunately, however, administering leptin to people does not effectively treat obesity. Thus, additional factors must also contribute to obesity.

Resistin, another fat cell signaling protein discovered recently, is so-named because too much of this hormone is thought to cause insulin resistance. When scientists gave mice a substance that inhibits resistin activity, their blood sugar level and insulin response improved. In fact, scientists initially discovered resistin as a result of some creative experiments to investigate how fat cells are affected by anti-diabetes drugs called TZDs, which are used to treat people. One of the results of adding a TZD drug to fat cells turns out to be decreased resistin production and improved response to insulin. Thus, resistin itself might now be useful as a target for the discovery of new anti-diabetes drugs. Another protein produced by fat cells, adiponectin, appears to connect obesity and diabetes in a way opposite to that of resistin — while too much resistin apparently causes insulin resistance, too little adiponectin may also be problematic. Scientists working on mouse models of obesity and type 2 diabetes recently found that giving extra adiponectin protein (made in the laboratory) to the mice caused them to become less insulin resistant, lowering their blood glucose levels to near normal. In other experiments, when scientists gave mice a TZD drug, the type of diabetes drug that lowers resistin levels, they found that the drug can also increase adiponectin levels. From other research in mice, it appears that adiponectin helps muscle cells burn more energy; it also reduces body weight. In people, studies suggest that overweight and diabetic patients do not produce enough adiponectin. Thus, adiponectin may also be a good target for new therapies. In light of these studies, the ominous link between obesity and diabetes may be a balance of the levels of several fat cell signaling proteins with different effects. As more is learned about fat cell signaling proteins, new drug therapies can be developed for obesity and diabetes.

While basic scientists are learning about what causes obesity and type 2 diabetes at the molecular level, clinical researchers are developing other measures to combat these conditions. Results from an exciting new study give us a way to battle the epidemic of obesity and type 2 diabetes. A major clinical study demonstrated that patients at risk of developing type 2 diabetes can prevent disease onset and improve their blood sugar through modest improvements in diet and exercise. These results are particularly important to minorities, who made up 45 percent of the study participants and are at increased risk

of developing diabetes. This study, called the Diabetes Prevention Program (DPP), identified overweight individuals suffering from pre-diabetes, a condition which, as discussed, increases the risk for type 2 diabetes. In the study, patients were assigned to one of three groups: intensive lifestyle intervention, medication, or placebo control. The latter two groups also received conventional information about diet and exercise. The intensive lifestyle intervention had a goal of reducing body weight and staying active with a minimum of 150 minutes of exercise a week. The lifestyle intervention worked the best; patients in this group reduced their risk of developing diabetes by 58 percent. Significantly, the intensive lifestyle intervention was highly effective for both genders and all ages and all racial and ethnic groups in the study. Patients in the medication group, who received the diabetes drug metformin, were also less likely to develop diabetes than the control group and they also lost weight. However, metformin, which reduced diabetes onset by 31 percent, was less effective than lifestyle intervention. This landmark study showed that, with instruction and encouragement, patients at high risk for diabetes could be successful in improving their diet and activity — with these relatively modest changes having a major impact on reducing the onset of diabetes. Efforts are now under way to develop more cost-effective methods of behavioral change. For example, researchers are studying whether similar results can be obtained when the intervention is given in a group setting or aided by efforts involving the Internet. Of particular importance is research to extend the duration of response to this intervention. Many programs are successful for short- term weight loss. The extended weight loss over three years in the DPP was particularly impressive and researchers are seeking ways to improve further on maintaining weight loss.

Photos: Weight-control Information Network (WIN).