

Strategic Plan for

NIH OBESITY RESEARCH

A Report of the NIH Obesity Research Task Force



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CONTENTS

EXECUTIVE SUMMARY1

BACKGROUND: OBESITY AND NIH RESEARCH9

NIH OBESITY RESEARCH GOALS, AND RESEARCH STRATEGIES FOR ACHIEVING THE GOALS

Overview23

Scientific Theme: Preventing and Treating Obesity Through Behavioral and Environmental Approaches To Modify Lifestyle27

Scientific Theme: Preventing and Treating Obesity Through Pharmacologic, Surgical, or Other Medical Approaches37

Scientific Theme: Breaking the Link between Obesity and its Associated Health Conditions43

Scientific Theme: Cross-cutting Topics48

A Snapshot in Time of a Dynamic Planning Process56

References for Statistical/Epidemiological Data57

APPENDIX A

Examples of NIH-supported Obesity Research Advances59

Examples of NIH Efforts to Bring the Results of NIH-supported Research to the Public and Healthcare Professionals66

APPENDIX B

Ongoing NIH Efforts69

The Strategic Plan for NIH Obesity Research is intended to serve as a guide for coordinating obesity research activities across the NIH and for enhancing the development of new efforts based on identification of areas of greatest scientific opportunity and challenge. Developed by the NIH Obesity Research Task Force with critical input from external scientists and the public, the Strategic Plan reflects a dynamic planning process and presents a multi-dimensional research agenda, with an interrelated set of goals and strategies for achieving the goals.

The major scientific themes around which the Strategic Plan is framed include: preventing and treating obesity through lifestyle modification; preventing and treating obesity through pharmacologic, surgical, or other medical approaches; breaking the link between obesity and its associated health conditions; and cross-cutting topics, including health disparities, technology, fostering of interdisciplinary research teams, investigator training, translational research, and education/outreach efforts. Through the efforts described in the Strategic Plan for NIH Obesity Research, the NIH will strive to facilitate and accelerate progress in obesity research to improve public health.

EXECUTIVE SUMMARY

Obesity has risen to epidemic levels in the U.S. It leads to devastating and costly health problems, reduces life expectancy, and is associated with stigma and discrimination. Obesity is a strong risk factor for such serious diseases as type 2 diabetes and heart disease; it is also a risk factor for certain cancers and is associated with depression and other medical conditions. More than 65 percent of U.S. adults are overweight or obese, with nearly 31 percent of adults—over 61 million people—meeting criteria for obesity. 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. Levels of childhood overweight have nearly tripled since 1970: approximately 16 percent of children and teens ages 6 through 19 are now overweight. 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 socioeconomic status. Left unabated, the escalating rates of obesity in the U.S. population will place a severe burden on the Nation's health and its healthcare system.

Obesity and NIH Research

On the surface, it may seem that the solution to the obesity epidemic is obvious: “Get people to eat less and exercise more.” The reality is that this change is very difficult to accomplish, and research is critical to address the issue successfully. Given the complexity and multiplicity of the forces driving the obesity epidemic, the NIH recognizes that it cannot, by itself, solve this major public health problem. However, the NIH can and must be a key contributor to solving the obesity problem through scientific research. Through its research mission, the NIH is seeking to capitalize on recent scientific discoveries to propel new efforts toward further understanding the forces contributing to obesity and toward developing strategies for its prevention and treatment.

The increase in obesity has been fueled by a complex interplay of environmental, social, economic, and behavioral factors, acting on a background of genetic susceptibility. Thus, the NIH supports a broad spectrum of obesity-related research, including molecular, genetic, behavioral, environmental, clinical, and epidemiologic studies. The challenges of today's obesity epidemic are daunting, yet the discoveries emanating from previous research investments offer unprecedented opportunities for new scientific research efforts to help meet these challenges.

NIH Obesity Research Task Force

Given the importance of the obesity epidemic as a public health problem, and its relevance to the mission of most of the NIH Institutes, Centers, and Offices (ICs), the NIH Director Dr. Elias Zerhouni established the NIH Obesity Research Task Force in April 2003, as a new effort to accelerate progress in obesity research across the NIH. The Task Force is co-chaired by the Director of the National Institute of Diabetes and

Digestive and Kidney Diseases (NIDDK), Dr. Allen M. Spiegel, and by the Acting Director of the National Heart, Lung, and Blood Institute (NHLBI), Dr. Barbara Alving. The members of the Task Force are representatives from these institutes and many other NIH components with relevant expertise. A key element of the NIH Director's charge to the Task Force is the development of a Strategic Plan for NIH Obesity Research.

The Strategic Plan for NIH Obesity Research: Informing the Process

Purpose and Formulation of the Strategic Plan

The purpose of the Strategic Plan for NIH Obesity Research is to provide a guide for coordinating obesity research activities across the NIH and for enhancing the development of new research efforts based on identification of areas of greatest scientific opportunity and challenge. The Strategic Plan represents a cohesive, multi-dimensional research agenda for addressing the problem of obesity. It includes short-, intermediate-, and long-term goals for basic, clinical, and population-based obesity research, along with strategies for achieving those goals that also range in timeframe. Building on scientific advances from previous NIH-supported efforts, the Strategic Plan seeks to maximize collaboration among the NIH ICs and capitalize on their expertise and interest in developing obesity research initiatives.

Importantly, the planning process was informed by input from external experts through interactions with NIH staff at scientific meetings, through meetings and workshops convened by NIH ICs for the purpose of obtaining research planning advice, and through presentations by the Co-chairs of the Task Force to external scientific and health advocacy organizations. For example, a "Think Tank" meeting on enhancing obesity research, held by the NHLBI, brought together a diverse group of stakeholders from the academic, consumer, and professional communities to provide research recommendations. Recent general scientific meetings offered a venue for NIH staff to glean external input and advice on obesity research planning. For example, a January 2003 Keystone meeting provided a means of tapping external scientific expertise regarding the pathogenesis and treatment of obesity. Later in 2003, the Co-chairs of the NIH Obesity Research Task Force gave the keynote lecture at the

Annual Scientific Meeting of the North American Association for the Study of Obesity (NAASO); this presentation afforded an opportunity to gain feedback from attendees on NIH obesity research efforts. An important advisory group from whom the NIH receives expert input on obesity is the NIDDK Clinical Obesity Research Panel (CORP), which is composed of leading external obesity researchers and clinicians. Additionally, strategies designed to achieve the goals of the Plan, in the form of initiatives, are reviewed and discussed by members of the ICs' National Advisory Councils, which are groups of prominent external scientific experts and lay leaders established by law and charter to provide advice to the ICs.

In addition to the external advice that the NIH receives through the avenues above, which continues to inform the obesity research planning process, the Strategic Plan document was circulated in draft form to invite comments from over 70 external individuals, including scientists with expertise in obesity research and leaders of voluntary and professional health advocacy organizations who could provide comments on behalf of these organizations. After receiving input from this effort (from nearly half of the individuals to whom NIH sent the draft, as well as from others with whom some of those individuals shared the draft), the revised Draft Strategic Plan for NIH Obesity Research was posted on the Internet to invite further scientific and public comment before production of a final version, which incorporates suggestions received during the final comment period.

The Strategic Plan is focused on research efforts that are funded by the NIH, specifically, those initiated by the NIH. Extramurally, the NIH supports both investigator-initiated research projects and research that results from NIH-initiated efforts—solicitations for grant applications and contract proposals. Although investigator-initiated research (projects proposed by individual scientists in areas that they identify) represents a substantial portion of the NIH funding portfolio and will continue to receive vigorous support in the future, it is not the intent of the Strategic Plan to cover the vast array of these studies. The NIH also supports an Intramural Research Program, which provides a unique resource for obesity research.

Through consultative efforts such as those described above, the NIH seeks to encourage investigators to apply their expertise toward: developing studies in areas of particular scientific opportunity or interest; addressing gaps in knowledge identified by the scientific community; overcoming barriers to advance research or to translate research results into public health and clinical practice; or pursuing other areas of research critical to the mission of the NIH.

A Dynamic Planning Process

As with any future-oriented plan, the Strategic Plan for NIH Obesity Research is intended to be dynamic. As new scientific opportunities arise from current research investments and accomplishments, the research planning process will evolve to build on these areas, thus accelerating research in the most promising directions to continue to meet the challenges of obesity.

Strategic Plan for NIH Obesity Research: Goals for NIH Obesity Research, and Strategies for Achieving the Goals

The Strategic Plan contains a cohesive set of interrelated goals for achievements in NIH obesity research. The goals are organized under the following four themes:

- ▶ **Research toward preventing and treating obesity through lifestyle modification.**
- ▶ **Research toward preventing and treating obesity through pharmacologic, surgical, or other medical approaches.**
- ▶ **Research toward breaking the link between obesity and its associated health conditions.**
- ▶ **Cross-cutting research topics, including health disparities, technology, fostering of multidisciplinary and interdisciplinary research teams, investigator training, translational research, and education/outreach efforts.**

For each of these four themes, goals for the short-, intermediate-, and long-term time horizons are presented, followed by a set of strategies for achieving the goals:

- ▶ **Research toward preventing and treating obesity through lifestyle modification.**

Under this theme, the goals and strategies for achieving them encompass identifying modifiable behavioral and environmental factors that contribute to the development of obesity in children and adults, and designing and testing potential intervention strategies. Research will build on the results of clinical trials that demonstrated successful behavioral and environmental approaches to lifestyle modification. The effects of specific modifications in diet and physical activity will be studied, as will modifications of environmental factors that promote over-consumption of food and sedentary lifestyles. Two examples of such research are work-site interventions to prevent obesity and studies of the “built environment” and its relationship to physical activity.

- ▶ **Research toward preventing and treating obesity through pharmacologic, surgical, or other medical approaches.**

Under this theme, the goals and strategies for achieving them encompass the continued elucidation of the molecules and biological pathways that regulate appetite, energy expenditure, and the storage of energy as fat; and accelerating the design and testing of treatment and prevention strategies. Research will include further genetic and other molecular studies. With respect to genetic research, some individuals are far more susceptible to developing obesity in a given environment than others. In rare cases of severe, early-onset obesity, this susceptibility results from a single genetic abnormality. Yet, more common forms of obesity are genetically complex, likely involving interactions of variations in multiple genes to increase susceptibility. The identification of genes involved in obesity will enhance efforts toward prevention and treatment. Through genetic studies and other molecular research, the NIH can identify potential new targets for drug development. These “targets”

would be the molecules and pathways involved in regulating energy balance—the balance between energy intake (through feeding) and energy expenditure (through physical activity and maintaining basic body functioning). Thus, research in these areas will contribute to the development of medical strategies that affect energy balance to help prevent or treat obesity.

▶ **Research toward breaking the link between obesity and its associated health conditions.**

Under this theme, the goals and strategies for achieving the goals encompass building on research that illuminates the connection between obesity and type 2 diabetes, cardiovascular disease, cancer, and other diseases. Major recent advances in the understanding of fat cell metabolism include the appreciation that fat cells secrete hormones that promote inflammation and hypertension. Understanding the different mechanisms of various body fat depots in causing insulin resistance (a precursor to diabetes) and other metabolic abnormalities is a fundamental question that must be addressed. Such research efforts as the recent creation of a bariatric surgery clinical research consortium and the formation of a network to study nonalcoholic fatty liver disease (a major new cause of liver failure associated with the obesity epidemic) will help to identify the mechanisms linking obesity to other serious health conditions, and will open the possibility of breaking the link between them.

▶ **Cross-cutting research topics, including health disparities, technology, fostering of multidisciplinary and interdisciplinary research teams and investigator training, translational research, and education/outreach efforts.**

The cross-cutting research theme encompasses several topics. First, of critical importance is a focus on the needs of specific populations, including children, racial/ethnic minorities who are disproportionately affected by obesity, persons living in conditions of lower socioeconomic status or who have low literacy, women, older adults, those with disabilities, and those who are extremely obese. For these special populations, goals and strategies to achieve the goals are found throughout the Strategic Plan as an integral part of obesity research. For example, the Strategic Plan includes a number of initiatives focused on childhood obesity, such as prevention in the pediatric primary care setting, and a multi-pronged school-based prevention trial. Because of the large racial/ethnic disparities in the incidence of obesity, a number of the efforts described in the Plan are directed at understanding the biologic and environmental factors contributing to such disparities and to addressing them in a culturally-sensitive manner. Also relevant to health disparities is communication of the results of scientific research. The Plan addresses the importance of tailoring education and informational efforts to different populations in culturally appropriate ways that provide effective communication.

Another cross-cutting area is fostering multidisciplinary and interdisciplinary research teams. Although the first two themes—on research toward preventing and treating obesity through lifestyle approaches and medical approaches—are listed separately, they are, in fact, interdependent. Effectively addressing the obesity epidemic will require the NIH to bridge the study of the behavioral/environmental causes of obesity and the study of the genetic/biologic causes. Ultimately, the NIH seeks to create a new interdisciplinary approach in which behavioral/lifestyle interventions are informed by a deeper understanding of the biologic and genetic factors, and vice versa. Successful prevention and treatment of obesity may well require combined medical and behavioral approaches in highly susceptible individuals. Given the multi-dimensional nature of the obesity epidemic, research efforts need to engage those with expertise in a variety of other areas, including, for example, economics, and fields relevant to the built environment and community design.

Translational research—progressing from basic science to clinical studies and from clinical trial results to community interventions—is another key cross-cutting research topic. For example, the NIH will study the effects of “social experiments” such as recent policy decisions in some schools concerning food offerings made available to the students. By obtaining data on the outcome of such policy decisions, the NIH can help policy makers develop further actions based on data rather than on assumptions.

To continue to advance progress in many obesity research areas, efforts to improve technologies will be valuable, as will efforts addressing the availability of resources for research. The NIH plans, for example, to encourage research to improve technologies for studying dietary intake and physical activity.

Finally, the NIH will continue activities to disseminate the results of research to the public and healthcare providers. It will be important that clear and appropriate communication, including messages and information about healthy eating, physical activity, and weight control strategies, reaches diverse audiences.

As noted in the Strategic Plan, the NIH will also partner with other agencies in the Department of Health and Human Services (HHS), other government departments, organizations in the private sector, and foundations and other public groups. By bringing data derived from rigorously reviewed and conducted studies to its partners, the NIH can contribute to framing the actions to address the obesity epidemic.

NIH Obesity Research Task Force Web Site

As one component of NIH efforts to enhance research on the major public health problem of obesity, the NIH Obesity Research Task Force has developed a new Web site (<http://obesityresearch.nih.gov/>). The primary purposes of this Web site are to help inform investigators about 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 Web site will reflect the dynamic and ongoing planning process for obesity research at the NIH. Additionally, the Strategic Plan for NIH Obesity Research was posted on the Web site in draft form — after having

already received substantial external input—in order to invite further scientific and public comment before publication of the Plan. Finally, although the focus of the Web site is on research, the site also includes links to other NIH Web sites that provide information to the public and health professionals on weight loss, nutrition, physical activity, and health problems associated with obesity.

Through the collective efforts of the NIH Obesity Research Task Force—and the ICs they represent—the NIH will strive to bolster obesity research to improve public health.

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BACKGROUND: OBESITY AND NIH RESEARCH

The Strategic Plan for NIH Obesity Research reflects a dynamic planning process at the NIH. The purpose of the Strategic Plan is to provide a guide for coordinating obesity research activities across the NIH and for enhancing the development of new research efforts based on identification of areas of greatest scientific opportunity. The Strategic Plan represents a cohesive, multi-dimensional research agenda for addressing the problem of obesity. As with any future-oriented plan, the Strategic Plan for NIH Obesity Research will evolve as research progresses and new opportunities and challenges emerge.

The introductory section of this document presents an overview of the health problem of obesity, followed by a section that addresses the role of NIH research as an important contributor to a broad-based national effort to address the obesity epidemic. Also described is the establishment of the NIH Obesity Research Task Force as a new effort to facilitate progress in obesity research across the NIH. Information is then given on the development of the Strategic Plan, including its formulation and purpose. Finally, the main sections of the document present the Strategic Plan, including goals for research achievements identified by the NIH, and research strategies to achieve those goals.

Background to the Health Problem of Obesity

Obesity is one of the most daunting health challenges of the 21st century. Left unabated, the escalating rates of obesity in the U.S. will place a severe burden on the Nation's health and its healthcare system.

Obesity is a major, chronic and relapsing health problem in its own right. It is also a strong risk factor for such serious diseases as type 2 diabetes, heart disease, and stroke, and is associated with certain cancers, osteoarthritis, liver disease, urinary incontinence, sleep apnea, depression and other medical conditions and can create significant disability (1). Obesity also shortens life expectancy: on average, people who are moderately obese have a life expectancy 2 to 5 years

less than those who are not overweight or obese; and those who are very severely obese have an average life expectancy 5 to 20 years less than those who are not overweight or obese (2). The stigma associated with overweight and obesity negatively impacts emotional well-being and may contribute to depression. In addition to the enormous impact on quality of life and increased risk of premature death associated with excess body weight, overweight and obesity also exact a substantial economic toll, with the combination of direct healthcare costs plus indirect costs, such as lost wages caused by illness, recently estimated at \$117 billion in the U.S. for the year 2000 (3).

The development and implementation of effective prevention and treatment strategies for obesity, through efforts of the NIH and others, would have a major positive impact on reducing risk for many devastating and costly diseases.

NIH evidence-based guidelines recommend moderate weight loss (i.e., 10 percent loss of initial body weight) for those who are overweight and obese (4). Even moderate weight loss results in improvements in glucose metabolism, lipid levels, and blood pressure.

Yet, even as the health problems associated with obesity become clearer, and even as Americans continue to make earnest efforts to lose weight—with about \$33 billion spent annually on weight-loss products and services—the levels of obesity continue to rise. The now-epidemic levels of overweight and obesity in the U.S. are a testament to the extraordinary difficulty of preventing weight gain, losing excess weight, and maintaining weight loss in today's environment. Not only is obesity a problem in the U.S., but it is also increasingly becoming a global health problem (5).

More than 65 percent of U.S. adults are overweight or obese, with nearly 31 percent of adults—over 61 million people—meeting criteria for obesity (1, 6, 7). These findings are based on assessments of body mass index (BMI), a measure of weight relative to height. In adults, overweight is defined as a BMI ≥ 25 , and obesity as a BMI ≥ 30 . Furthermore, assessments of different categories of BMI in the population have found that, while the population in general has shown increases in BMI, the greatest increases observed over approximately the past two decades have been in the highest BMI category—those with extreme obesity (also known as severe or morbid obesity), defined as a BMI ≥ 40 (8). The prevalence of extreme obesity is estimated at 4.7 percent of U.S. adults (6). These results likely reflect the interaction of high

genetic susceptibility to obesity with environmental factors that promote weight gain. These findings have alarming implications for public health, as those who are severely obese also are most at risk for serious health problems. Although rates of overweight and obesity have been increasing in many segments of the population, overweight and obesity disproportionately affect racial and ethnic minority populations, especially minority women (3). Women of lower socioeconomic status are also more likely to be obese than those of higher socioeconomic status (3).

Levels of childhood overweight have nearly tripled since 1970: approximately 16 percent of children and teens ages 6 through 19 are now overweight, with an additional 15 percent considered at risk for overweight (7, 9). For children, overweight is defined as a BMI ≥ 95 th percentile for age and gender based on previous national surveys, and at risk for overweight is defined as a BMI 85th to <95 th percentile. There is not yet an acceptable BMI cut-point to identify obesity in children and adolescents. Within this Strategic Plan document, the terms overweight and obesity are used interchangeably for children. Among some groups of the population the increases have been even more alarming: for example, the prevalence of overweight among African American girls ages 6 to 11 years has quadrupled since 1970 (10). Thus, even more emphasis is needed on research on childhood weight problems. The levels of pediatric overweight have ominous implications for the development of serious diseases, both during youth and later in adulthood. For example, type 2 diabetes was once viewed as a disease of older adults, but is now increasingly reported in children—a trend that is

believed to be related to increasing rates of overweight in children. Type 2 diabetes was found to represent 8 to 45 percent of newly-diagnosed diabetes in children and adolescents in North America in the 1990s (11). The escalation in childhood obesity also may well be a harbinger of enormous future demands on the U.S. healthcare system.

Essentially, obesity results from an energy imbalance. The body needs a certain amount of energy—supplied by calories from food—for such basic life functions as breathing, and for walking, playing sports, and all other physical activities. Body weight is maintained when the number of calories eaten equals the number of calories the body expends, or burns, to maintain life and support physical activity—a state of “energy balance.” When calories consumed exceed calories burned, the energy balance is tipped toward weight gain and obesity. Likewise, weight is lost when energy expenditure exceeds caloric intake. However, achieving energy balance (maintaining weight) or tipping the balance toward weight loss can be extremely difficult.

Because of the widespread prevalence of obesity and because sustained weight loss is so difficult to achieve, the development of effective strategies to prevent inappropriate weight gain in the first place is critical, particularly for children who may otherwise face a lifetime of health problems. Given the current numbers of adults and children in the U.S. who are overweight or obese, the development of new and effective treatment strategies is also imperative. Lifestyle changes resulting in moderate weight loss can have substantial health benefits, but long-term maintenance of weight loss remains a difficult challenge. Drug therapy, in conjunction with lifestyle changes, can also help with weight loss and maintenance, but currently, few weight loss medications are approved for long-term use; those approved have only modest efficacy; and none are approved for use in children younger than 16. Surgical treatment of obesity (bariatric surgery) results in substantial weight loss, which in many cases is sustained over the long term. In addition, this

weight loss results in complete resolution or marked improvement in many obesity-related comorbid conditions. However, surgical treatment is appropriate only for those with severe obesity, and carries with it the possibility of significant complications (including death), as well as the need for life-long medical follow-up. Thus, goals of obesity prevention and treatment would benefit greatly from continued exploration of behavioral and medical (including surgical) interventions. Further research into the role of genetics in the development of obesity and its potential usefulness for informing interventions tailored to specific individuals will be beneficial. Understanding basic biological mechanisms can inform both behavioral lifestyle interventions, as well as medical and other biological interventions. Concomitantly, environmental factors that promote obesity also warrant increased research.

Research has shown that genetic factors clearly play an important role in predisposing individuals to obesity. However, the dramatic increase in prevalence of obesity over the past two decades has been largely attributed to the interaction of genetic susceptibility with behavioral changes and factors pervasive in our current “obesogenic” environment that promote increased caloric intake and physical inactivity. Potential factors include: technological advances that have been incorporated in the workplace and in activities of daily living so as to reduce the need for physical labor; increased time spent in sedentary activities such as television watching and computer use; a bountiful food supply with abundant choices of relatively inexpensive, calorically-dense food products that are convenient and taste good; and an increase in the sizes of food portions served not only in restaurants but also in the home. Not all foods, however, are equally available and affordable. A potential contributing factor to minority health disparities in obesity, suggested by recent research, may be a relatively limited availability of healthful foods such as fresh fruits and vegetables in geographic areas of high minority concentration that are not as economically advantaged as other areas. Panning outward to encompass a larger view of the

environment reveals additional factors that may contribute to obesity—components of the “built environment.” These factors include, for example, the greater distances between home, work, school, and stores in sprawling suburban areas that necessitate travel by car rather than by foot, and an absence of sidewalks in many communities. Issues such as the effect of neighborhood crime on the choice of whether to walk

or let children play outdoors could also contribute to decreased physical activity. Research is needed to identify the extent to which each of these factors may contribute to the problem of obesity. Research on strategies to modify—or compensate for—a number of these environmental factors will likely be necessary in order to make individual behavior changes in food intake and activity more achievable and sustainable.

Although genetic factors are believed to contribute substantially to the predisposition toward obesity, it is unlikely that our genes could have changed quickly enough to account for the rapid rise in obesity in the U.S. Thus, the dramatic increase in obesity prevalence over the past two decades is considered a consequence of the interaction of genetic susceptibility with behavioral changes and with factors pervasive in today's environment that promote increased caloric intake and sedentary lifestyles.

The field of obesity research sees enormous scientific opportunities in the near future. For the first time in history, the neural pathways of body weight regulation are being elucidated, including the powerful roles of leptin, ghrelin, peptide PYY₃₋₃₆, and neuropeptide Y. The next stages of the Human Genome Project hold the promise to integrate the molecular understanding of normal and abnormal body weight regulation. Fresh insights into the significant racial and ethnic disparities in obesity and its comorbid conditions are foreseen. With such information, more precise and informed prevention strategies, behavioral interventions, pharmacology, and surgical interventions can be developed and tested. Such prevention and treatment strategies will give rise to questions of economic efficiency and legislative and regulatory approaches.

What Is Obesity?

The principal characteristic of obesity is excess adipose (fat) tissue. There are, however, different types of fat and different locations for fat in the body. For example, excess visceral fat (fat surrounding the internal organs in the abdomen) appears to be a better predictor of obesity-associated health problems than the amount of total body fat. With respect to measuring obesity, BMI is one currently accepted and widely-used measure. It has many advantages, but like other measures, it is not perfect. One limitation of BMI is that it does not distinguish between weight from fat and weight from muscle or bone. BMI also does not identify the distribution of body fat. Additionally, some research suggests that the currently-accepted standard cut-off point for defining obesity based on BMI may not reflect the same risk for further health consequences in all racial/ethnic groups.

Research has shown that obesity is associated with diseases such as type 2 diabetes, heart disease, and cancer, and is also associated with premature death. Among the metabolic consequences associated with obesity are hypertension, which is relevant to cardiovascular disease, and insulin resistance, which is a characteristic of—and precursor to—type 2 diabetes. Fat cells, in fact, produce certain proteins whose levels have been associated with insulin resistance, providing possible molecular links between obesity, insulin resistance, and diabetes. Adipose tissue, in addition to secreting hormones that regulate energy balance, also produces proteins that promote inflammation, which is associated with heart disease and other conditions. However, not every obese person develops such diseases as diabetes. Thus, the nature of the associations between obesity and its metabolic and health consequences—such as the diseases mentioned above, as well as general fitness—are important areas for further study.

In addition to being associated with many other diseases, obesity itself has been called a disease, for example, in the Consensus Statement developed by a non-Federal panel of experts convened by the NIH for a Consensus Development Conference held in 1985 (12), and by the NIH *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults*, published in 1998 (4). Debate continues on this topic.

Finally, obesity can result from a variety of different causes. As discussed, a multitude of factors interact to contribute to obesity, from inherent biological traits (stemming from genetic factors that differ between individuals) that are relevant to body weight regulation, to environmental and socioeconomic factors, to behavioral factors—which may have both molecular and environmental influences. It is likely that the relative influences on obesity of genetic, behavioral, and

environmental factors exist on a spectrum. There is also a wide variety of different types of these factors. Examples of environmental influences on obesity were discussed previously. With respect to genetics, there are known abnormalities in single genes, including those affecting the gene for the hormone leptin or the gene for the melanocortin 4 receptor protein, that cause the development of early onset, severe obesity. Although the obesity that results from either of these is clearly a serious disease, these genetic abnormalities are rare, and the nature of the genetic variations that may contribute to more common forms of obesity is not yet clear. It is thought that multiple genetic variations interact in a complex way to contribute to more common forms of obesity. An interesting view that has been expressed regarding the genetic basis for more common forms of obesity is the “thrifty gene hypothesis.” That is, it is thought that because our ancestors lived in environments with more risk of starvation from famine, and greater need for physical exertion to survive, a genetic predisposition to efficient storing of fat (and hence, energy) was actually advantageous. In a current environment in which calorie-rich food is plentiful and life can be more sedentary, the ability to accumulate fat efficiently is no longer beneficial. The variety and complexity of interacting causes of the obesity epidemic today indicate the importance of developing multiple treatment and prevention strategies, as different strategies will likely work best for different people.

Role of the NIH in Addressing the U.S. Obesity Epidemic: Research Contributions

The increase in prevalence of obesity has been fueled by a complex interplay of behavioral, sociocultural, economic, and environmental factors, acting against a backdrop of genetic and other biological factors. Combating the pressing public health problem of obesity thus requires broad-based national efforts, including diverse contributions of the NIH, other government agencies, researchers (including those supported by the NIH and by other sources), the healthcare delivery system, professional organizations, advocacy groups, industry, community-based organizations, public policy makers, and others. The Strategic Plan for NIH Obesity Research focuses on the role of NIH research as one component of multi-faceted national efforts.

Research aimed at pinpointing the underlying causes of a disease, or at potentially contributing or exacerbating factors, is critically important in developing effective approaches to prevention and treatment. Given the ominous links between obesity and type 2 diabetes, cardiovascular disease, cancer, osteoarthritis, depression, and numerous other serious health conditions, NIH-supported obesity research plays a vital role in multiple efforts to improve public health.

Thus, the NIH pursues a broad spectrum of basic, clinical, and translational research avenues related to obesity. These efforts range from basic science studies addressing its causes and the underlying biologic mechanisms that link obesity to serious diseases; to clinical research on prevention strategies and treatments—for children as well as adults—encompassing behavioral and environmental interventions in a variety of settings, and medical (drug-based or surgical) strategies; to translational research that tests potential interventions that may promote widespread application of effective treatments or prevention approaches. The NIH further seeks to pursue the development of enabling technologies, to foster multi-disciplinary and interdisciplinary research teams, to enhance training opportunities for investigators, and to disseminate research results and engage different public and health professional audiences in the understanding and use of obesity communication (information and education). The results of NIH-supported research may also provide a scientific foundation for public policy related to delivery of healthcare services as well as for the development and delivery of public health programs.

To accelerate progress toward obesity prevention and treatment, it is imperative to advance research on molecular and physiologic factors that may contribute to obesity, as well as research on obesity-associated diet and physical activity behaviors. Not only can molecular and physiologic research complement behavioral research, but each discipline can also provide important insights into the other.

There is no single cause of all human obesity—factors involved include, for example, behavioral, sociocultural, socioeconomic, environmental, physiologic, and genetic. Thus, no single prevention or treatment strategy is likely to work for everyone. Behavioral or environmental interventions may be sufficient for some, while the addition of drugs or surgical procedures that facilitate weight loss may be necessary for others. A better understanding of genetic susceptibilities to obesity and the interaction of genetic factors with behavioral and medical therapies can lead to targeted strategies for prevention and treatment. Neurobiologic research can cast new light on the molecular underpinnings of behaviors, including eating and physical activity. Additionally, a better understanding of the mechanisms for changing behavior and maintaining that change, as well as increased understanding of the physiology underlying behavior

change and its maintenance, might help in the design of future, more effective behavioral interventions. Moreover, behavioral strategies found effective for promoting weight loss—or preventing weight gain—may also facilitate adherence to a prescribed regimen of medical weight loss treatments.

Differences in genetic, environmental, cultural, and social conditions affect obesity trends and can thus be better understood through careful research in diverse populations and settings—including populations in other countries. Obesity represents a serious and growing phenomenon in both developed and developing countries. Scientific opportunities for further exploration also exist in the global arena and include research into contributing causative factors and potential interventions, as well as research training.

As molecular and genetic studies continue to reveal the elaborate network of biological molecules that control appetite and energy expenditure, this research also serves to underscore that obesity does not result from a simple lack of will power. Rather, obesity results from a complex interaction among genes, physiology, behavior, sociocultural factors, and the environment.

Collaborative Efforts Between the NIH, Other Federal Agencies, and Public and Private Organizations

There is increasing discussion concerning efforts to address prevention and treatment of overweight and obesity among the various Federal agencies. Initiatives being developed within agencies tend to emphasize the complementary nature of their goals and objectives and to minimize duplication. As initiatives are developed, announced, and reviewed, there is increasing participation in the process by staff from various agencies. Opportunities are available to provide joint support for efforts, and a number of the research efforts described in this Strategic Plan involve collaborations between the NIH and other Federal agencies. For example, the Centers for Disease Control and Prevention (CDC) has been involved in the cost-effectiveness component of several NIH-led clinical trials relevant to overweight and obesity. The CDC also participated in a recent NIH conference to plan new efforts to translate diabetes and obesity research from clinical trial settings to the community, and a recent workshop to plan a new community outreach effort on achieving a healthy weight. As an example of an ongoing venue for communication among agencies, the NIH Nutrition Coordinating Committee has liaison membership from a number of Federal agencies and meets regularly to discuss topics related to obesity and nutrition, including plans for research efforts and workshops.

NIH staff also participate in a number of interagency efforts relevant to obesity. For example, NIH representatives have contributed to efforts spearheaded by the Department of Health and Human Services, which include the Secretary's recently-formed Prevention Steering Committee Working Group on Obesity, and the Secretary's Roundtable on Obesity/Nutrition, a meeting held in 2003. Additionally, the NIH Obesity

Research Task Force has met with representatives from the U.S. Department of Agriculture (USDA), and future interactions between the Task Force and the U.S. Surgeon General are being discussed. The NIH also participates in the interagency "Healthy People 2010" public health planning efforts relevant to nutrition and overweight, as well as other health topics.

Effective knowledge translation occurs in an environment where appropriate, understandable communication flows in all directions—among researchers, practitioners, patients, and the public. Creating a culture of meaningful information and communication exchanges is critical if preventing and treating obesity through behavioral and environmental approaches are to be fully realized. Using results from its funded research projects—a number of which involve collaborations with other Federal agencies or private organizations—the NIH develops evidence-based guidelines and educational materials to facilitate translation of knowledge and effective interventions into clinical healthcare services and public health programs. To enhance such translation, the NIH works with Federal and private partners. Examples of successful public/private partnerships that promote healthy eating behaviors and physical activity include the NHLBI Obesity Education Initiative, the NCI 5-A-Day Program for Better Health, and the NIDDK/CDC National Diabetes Education Program. Research on how best to translate efficacious interventions into clinical service delivery and public health programs (one form of "translational research") is critically needed as a complement to the research that provides the science base for the interventions. The NIH plays an important role in supporting effectiveness and

clinical translation research, as do other Federal agencies. Clinical translation research and collaborative partnerships will contribute to controlling the obesity epidemic at the population level.

Further pursuit of collaborations and interrelationships with various industries may prove fruitful. However, clear guidelines need to be established to avoid inappropriate endorsements of specific programs and products, or other potential conflicting interests. One type of complementary effort between Federal and private entities involves drug development, in which the pharmaceutical industry is able to build on

research from academia to move basic research discoveries into the realm of drug development efforts. As discussed, the NIH partners with private organizations in research dissemination and education activities. Other types of collaborations that may be useful for enhanced exploration include, for example, partnerships to facilitate research on lifestyle intervention strategies designed to be carried out at work-sites, and potential research-based collaborations with food or fitness industries. Such collaborations may be valuable both to research endeavors and to the dissemination of research-based information to the public and healthcare professionals.

Past Investments, Current Efforts, and the Research Planning Process

As a strategic planning tool, this document is primarily focused on future research directions for the NIH. Yet, many ongoing studies, as well as extraordinary scientific opportunities for the future, have been made possible by discoveries emanating from previous research endeavors. Thus, although a comprehensive review of the vast number of earlier research findings is beyond the scope of a forward-looking document, selected NIH-supported research advances are highlighted in Appendix A. These are intended to serve as examples to illustrate the expanding foundation upon which current and future NIH research efforts are being developed as part of the strategic planning process.

In addition, highlights of numerous ongoing obesity research efforts, supported by the NIH, are presented in Appendix B. This research will help to achieve goals set forth in the planning process, in part through the direct impact of scientific findings that arise from these efforts. These efforts will also propel future research planning toward achieving obesity research goals by building a critical knowledge base, illuminating those paths to new discovery that appear most promising, and potentially opening entirely new avenues for exploration.

NIH Obesity Research Task Force

Numerous components of the NIH support obesity research. Recognizing that obesity is escalating as a public health problem, a number of Institutes, Centers, and Offices (ICs) of the NIH have recently taken new actions to augment their obesity research portfolios, supporting extramural research at academic and medical institutions throughout the U.S., and intramural studies on the NIH campus and satellite facilities. The complexity of the problem of obesity dictated that the NIH take a more collaborative and multidisciplinary approach. Thus, the NIH Director, in the Spring of 2003, created the NIH Obesity Research Task Force as a new effort to facilitate progress in obesity research

across the NIH, enhancing and synergizing the efforts of individual ICs.

The Task Force is co-chaired by the Director of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and by the Acting Director of the National Heart, Lung, and Blood Institute (NHLBI), and its membership consists of representatives from these and numerous other NIH ICs, listed below. By drawing upon the rich and diverse expertise of their respective ICs, the Task Force members bring a wealth of knowledge and insights from numerous disciplines to bear on obesity research planning across the NIH.

National Institute of Diabetes and Digestive and Kidney Diseases

National Heart, Lung, and Blood Institute

National Cancer Institute

National Human Genome Research Institute

National Institute on Aging

National Institute on Alcohol Abuse and Alcoholism

National Institute of Arthritis and Musculoskeletal and Skin Diseases

National Institute of Biomedical Imaging and Bioengineering

National Institute of Child Health and Human Development

National Institute of Dental and Craniofacial Research

National Institute on Drug Abuse

National Institute of Environmental Health Sciences

National Institute of Mental Health

National Institute of Neurological Disorders and Stroke

National Institute of Nursing Research

National Center for Complementary and Alternative Medicine

National Center on Minority Health and Health Disparities

National Center for Research Resources

NIH Division of Nutrition Research Coordination

NIH Fogarty International Center

Office of Behavioral and Social Sciences Research

Office of Dietary Supplements

Office of Disease Prevention

Office of Research on Women's Health

The NIH Director's charge to the Task Force includes developing a Strategic Plan for NIH Obesity Research, monitoring implementation of the plan and reporting progress to the NIH Director and IC Directors, and serving as a point of contact between the NIH and relevant external agencies. A key element in framing the Strategic Plan for NIH Obesity Research is input

from extramural scientists and the public. The Strategic Plan is based on the identification of areas of greatest scientific opportunity and challenge, and seeks to maximize collaboration among the ICs and to capitalize on their expertise in developing initiatives. A component of the planning process includes the development of a coordinated Intramural obesity research program.

Development of the Strategic Plan for NIH Obesity Research

Purpose of the Plan

The purpose of the Strategic Plan for NIH Obesity Research is to provide a guide for coordinating obesity research activities across the NIH and for enhancing the development of new NIH research efforts based on identification of areas of greatest scientific opportunity and challenge. The Strategic Plan represents a cohesive, multi-dimensional research agenda for addressing the problem of obesity. As with any future-oriented plan, the Strategic Plan for Obesity Research is intended to be dynamic. As new scientific opportunities arise from current research investments, the research planning process will evolve to build on these areas, thus accelerating research in the most promising directions to continue to meet the challenges of obesity.

By maximizing collaboration among NIH's Institutes, Centers, and Offices, the planning process capitalizes on their range of expertise in developing research initiatives:

- ▶ To continue to identify the causes—genetic (and other biologic), behavioral, and environmental—of obesity;
- ▶ To increase knowledge—at molecular, cellular, and integrative body systems levels—of the pathways by which obesity is linked to health problems;

- ▶ To explore, through research, such areas as public policy, economics, communication, and the built environment, which impact on what has been termed an “obesogenic” environment;
- ▶ To bolster resources for research by fostering the development of enabling technologies and by encouraging the collaborative efforts of multidisciplinary and interdisciplinary teams of scientists;
- ▶ To use findings emanating from the research efforts above to generate and test innovative individual and population level approaches for preventing and treating obesity;
- ▶ To develop potential therapeutic approaches for reducing the risks or health effects of obesity-associated diseases, even in the absence of weight loss;
- ▶ To disseminate knowledge of successful prevention and treatment strategies from research settings to the community;
- ▶ To respond to requests from the public and policy makers for NIH scientific comments on issues related to obesity.

Formulation of the Plan

A key element of the NIH Director's charge to the NIH Obesity Research Task Force was the directive to develop an NIH-wide Strategic Plan for obesity research. The current plan responds to that charge. It attempts to incorporate the wealth of insights from the diverse areas of the NIH represented by participating Institutes, Centers, and Offices.

External input to inform the planning process and development of the Plan

Importantly, the planning process was informed by input from external experts through interactions among NIH staff at scientific meetings, through meetings and workshops convened by NIH ICs for the purpose of obtaining research planning advice, and through presentations by the Co-chairs of the Task Force to external scientific and health advocacy organizations. An example of a major meeting convened by the NIH in 2003 was a "Think Tank" on enhancing obesity research. This meeting, held by the NHLBI, brought together a diverse group of stakeholders from the academic, consumer, and professional communities to provide research recommendations. Among recent general scientific meetings that offered a venue for NIH staff to glean external input and advice on obesity research planning was a January 2003 Keystone meeting on pathogenesis and treatment of obesity. Later in 2003, the Co-chairs of the NIH Obesity Research Task Force gave the keynote lecture at the Annual Scientific Meeting of the North American Association for the Study of Obesity (NAASO); this presentation afforded an opportunity to gain feedback on NIH obesity research efforts from the meeting attendees. An important advisory group from whom the NIH receives expert input on obesity is the NIDDK Clinical Obesity Research Panel (CORP). The CORP (formerly, the "National Task Force on Prevention and Treatment of Obesity") is a group of leading external obesity researchers and clinicians that provides advice on

important clinical research needs related to obesity prevention and treatment. The CORP also serves in an advisory capacity to the NIDDK's Weight-control Information Network, which produces and disseminates science-based information on topics related to obesity. Additionally, strategies designed to achieve the goals of the Plan, in the form of concepts for new or expanded initiatives, are reviewed and discussed by members of the National Advisory Councils for the various ICs; these Councils are groups of prominent external scientific experts and lay leaders established by law and appointed by charter by the Secretary, HHS, to provide a second-level of peer review and broad science policy advice.

In addition to the external advice that the NIH receives through the avenues above, which continues to inform the obesity research planning process, the Strategic Plan document was circulated in draft form to invite comments from over 70 individuals external to the NIH, including scientists with expertise in obesity research and leaders of voluntary and professional health advocacy organizations in order to solicit input. After receiving responses from this effort (from nearly half of the individuals to whom NIH sent the draft, as well as from others with whom some of those individuals shared the draft), the Task Force prepared a revised draft of the Strategic Plan for NIH Obesity Research for posting on the Internet to invite further scientific and public comment before production of a final version. The current version of the Strategic Plan incorporates suggestions received during the final comment period. A broad range of expertise was represented among the external individuals and organizations providing input on the draft Strategic Plan document. Those providing input included, for example, scientists at universities and other research settings, physicians and other health care professionals, representatives of medical professional and advocacy organizations, and members of the lay community. The following are examples of the areas of expertise of those who provided input: endocrinology and metabolism, energy balance, body

composition, nutrition, physical activity, diet and exercise interventions, behavioral research, pharmacotherapy, bariatric surgery, genetics, lipid metabolism, psychosocial effects of obesity, cardiovascular disease, cancer, family medicine, nursing, pediatric obesity, pediatric diabetes, pediatric gastroenterology, eating disorders, urban development, epidemiology, obesity and overweight in minority populations, and women's health.

Research support and the peer-review system

Support of the research efforts described by the Plan depends upon the long-standing peer-review system to ensure that resources are deployed to meritorious research projects. Grant applications are first evaluated by external experts in relevant fields. These experts may be assembled by the NIH Center for Scientific Review, and may also be convened, as appropriate, by individual ICs to evaluate applications submitted in response to specific solicitations. Procedures exist for ensuring that study sections or other review panels comprise individuals with necessary expertise. After this first evaluation, the applications are subsequently assessed by the ICs' National Advisory Councils for final funding decisions. Research efforts are supported within the context of resource availability.

Focus of the research efforts covered in the Strategic Plan

This Strategic Plan is focused on research efforts that are supported by the NIH, specifically, those initiated by the NIH. The NIH supports both investigator-initiated research projects and research that results from NIH-initiated efforts. NIH-initiated efforts typically take the form of solicitations called "Requests for Applications" or "Program Announcements" for grants and "Requests for Proposals" for contracts. Although investigator-initiated research—projects proposed by individual scientists in areas that they identify—represents a substantial portion of the NIH

funding portfolio and will continue to receive vigorous support in the future, it is not the intent of this document to cover the vast array of these studies. An Appendix to the Strategic Plan highlights examples of past obesity-related scientific advances supported by the NIH and includes examples of advances from investigator-initiated research. However, the other sections of the document focus on NIH-initiated efforts.

Through its broad consultative efforts, the NIH encourages investigators to apply their expertise toward: developing studies in areas of particular scientific opportunity, interest, or challenge; addressing gaps in knowledge identified by the scientific community; overcoming barriers to the advancement of research, or to the translation of research results into public health and clinical practice; or pursuing other areas of research critical to the mission of the NIH.

Informing Researchers and Others about Future NIH Obesity Research Efforts

Although a strategic planning document is necessarily a "snapshot in time" of research goals, opportunities, and challenges, the NIH has taken steps to facilitate future research efforts in a sustained and dynamic way by creating a Web site focused on the development of NIH obesity research to complement the Strategic Plan. A key objective of the Web site is to aid investigators in pursuing obesity research by maintaining an up-to-date list of NIH funding opportunities that includes initiatives and other research efforts as they are launched. The Web site also includes information on NIH-sponsored scientific meetings, conferences, and workshops in a variety of areas relevant to obesity research. Additionally, although the focus of this Web site is on research, the site also includes links to other NIH Web sites 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.

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NIH OBESITY RESEARCH GOALS, AND RESEARCH STRATEGIES FOR ACHIEVING THE GOALS

OVERVIEW

The strategic planning process included the development of a cohesive set of interrelated goals for achievements in basic, clinical, and population-based NIH obesity research, along with strategies for achieving those goals. Information on considerations in the development and presentation of these goals and strategies within this Strategic Plan is provided in this section.

Structure of the Strategic Plan

This Strategic Plan has four major scientific themes, around which chapters are framed.

The themes are:

- ▶ Research toward preventing and treating obesity through lifestyle modification.
- ▶ Research toward preventing and treating obesity through pharmacologic, surgical, or other medical approaches.
- ▶ Research toward breaking the link between obesity and its associated health conditions.
- ▶ Cross-cutting research topics, including health disparities, technology, fostering of multidisciplinary and interdisciplinary research teams, investigator training, translational research and education/outreach efforts.

Relevant to these themes, goals and strategies for achieving them are presented as follows:

Goals

- ▶ Short-term goals
- ▶ Intermediate-term goals
- ▶ Long-term goals (specific and overarching)

The goals are organized into relative timeframes based on the time at which research would be expected to have achieved the goal, rather than the time point when the research would begin. Thus, short-term goals are those expected to be achievable with today's technology and knowledge base. Intermediate- and long-term goals encompass, for example, those requiring research projects that must last for a number of years (such as a clinical trial on the long-term effects of a weight-loss intervention), as well as research whose initiation will be predicated on the results of endeavors not yet completed.

Among the long-term goals are “overarching goals;” these are presented for the first three chapters. These goals have the longest time horizon and highest expected difficulty for attainment. Because of their strategic importance, they are highlighted in bold at the end of the goals sections for each of these chapters.

Strategies for achieving the goals

- ▶ Ongoing efforts
- ▶ Plans under development
- ▶ Concepts for future research

The strategies for achieving the goals reflect a coordinated and proactive research agenda encompassing a broad spectrum of research disciplines. As with the goals, the strategies for achieving them range in timeframe. Ongoing efforts encompass research that is already under way (described in Appendix B).

Plans under development include research expected to be initiated in the very near term as a result, for example, of research solicitations that have been recently-published or that are expected to be issued soon. Concepts for future research are strategies in earlier stages of development for implementation further in the future. Because of the nature of different research projects, among the strategies to achieve the goals, some recently-launched studies may not yield their key results for a number of years, for example, while some efforts not yet begun may bear fruit within a shorter period of time.

An Interdisciplinary Vision

Although the first two themes—on research toward preventing and treating obesity through lifestyle approaches and medical approaches—are listed separately, they are, in fact, interdependent. Effectively addressing the obesity epidemic will require the NIH to bridge the study of the behavioral/environmental causes of obesity and the study of the genetic/biologic causes. Ultimately, the NIH seeks to create a new interdisciplinary approach in which lifestyle interventions are informed by a deeper understanding of biologic and genetic factors, and vice versa. Successful prevention and treatment of obesity may well require combined medical and behavioral/environmental approaches in highly susceptible individuals.

Health Disparities and Research Planning

A critical component of the planning of research strategies relating to all of the goals is the consideration of issues relating to health disparities in obesity.

Some racial and ethnic minority populations, including African Americans, Hispanics, and American Indians, are disproportionately affected by obesity, beginning in childhood. Racial and ethnic differences exist not only in incidence and prevalence of obesity, but also in access to care, response to treatment, and susceptibility to the health effects of obesity. Therefore, a broad research agenda that spans basic biology through development, evaluation, and translation of culturally-appropriate community-based prevention efforts targeting diverse populations will need to be developed.

Socioeconomic status is also related to the incidence and prevalence of obesity, such that the poor are disproportionately affected by obesity, regardless of race/ethnicity. Research is needed to further understand the impact of socioeconomic status on the development of obesity and its related medical conditions. Disparities in the availability of services may also contribute to obesity; for example, those who are poor also have less access to healthcare. Thus, the research agenda should also include studies that identify effective strategies for overcoming socioeconomically-induced barriers to prevention and treatment. Differences in literacy and access to information also have been suggested as a causal factor for health disparities. Participatory approaches based on community engagement are essential and could be developed through the application of communication theories and methods.

In addition to addressing disparities related to race/ethnicity and socioeconomic status, it is important to explore sex/gender differences in development of obesity and in responses to interventions. For example, African American women are much more likely than African American men to be obese. Understanding gender-specific physiologic and behavioral factors that increase risk at different life stages (such as pregnancy or menopause) should provide insights into opportunities for prevention strategies, as well as novel treatments.

The health risks of obesity, as well as the type, timing, and potential effects of its treatment, are not uniform throughout the lifespan. Among children, certain “critical periods” may impact susceptibility to obesity and its complications, as well as offer opportunities for more effective intervention targeted to developmental stage. The impact of obesity on functional status in older adults, as well as the benefits and risks of weight loss in this population, is not well-studied.

Persons with extreme obesity constitute another understudied group in biomedical research, including obesity research, despite the disproportionate burden on health and quality of life posed by their obesity. The role of disability in obesity—as both a contributing factor to the development of obesity, as well as a consequence—also deserves special attention and commitment in research to eliminate health disparities.

A Dynamic Planning Process

Finally, it must be recognized that research planning is a dynamic process. Research strategies developed to achieve goals will necessarily evolve, and paths for future research will depend upon the outcomes of current studies. The results of ongoing research will bring new knowledge to better inform future investments—and, as is often the case with scientific research—may also lead to serendipitous discoveries or open exciting and as-yet-unimagined new opportunities for the future.

Strategic planning is an ongoing process that requires regular re-evaluation and assessment of research programs and initiatives, needs, and opportunities.

SCIENTIFIC THEME:

Preventing and Treating Obesity Through Behavioral and Environmental Approaches To Modify Lifestyle

Research Topic

Identifying areas for intervention—assessing obesity-related knowledge, behaviors, environments, and genetic variation and other biological characteristics of the U.S. population; and determining behavioral and environmental factors that contribute to weight gain and obesity

The development of effective strategies for obesity prevention and treatment based on improving physical activity and diet may be enhanced by increased understanding of the knowledge, behaviors, genetic variation and other biological characteristics of the U.S. population that may contribute to obesity and influence its treatment and prevention. For example, understanding how health recommendations are perceived by the public and their healthcare providers can inform the design of approaches to implement diet and physical activity interventions in ways that will be most comprehensible—and compelling. Increased research may establish a better understanding of family, psychosocial, and cultural factors that contribute to these behaviors. Behavioral theories and conceptual models of behavior change can be drawn upon to help identify factors that influence perceptions, beliefs, attitudes, motivation, and psychosocial mediators and pathways. Such research could examine, for example, how recommendations are perceived by the public and healthcare providers, the role of social support in motivation, and the influence of past experiences on self-efficacy for behavior change.

A complex interplay of environmental and behavioral factors, often interacting with genetic susceptibility to weight gain, is likely driving the dramatic increase in obesity prevalence. Thus, goals of obesity prevention and treatment would benefit from strengthened understanding of individual eating and exercise behaviors that contribute to weight gain, from intensified exploration of the environmental factors that promote unhealthy behaviors in broad segments of the population, and from building knowledge of genetic variation associated with obesity.

Research focused on behavior and the environment should include various types of studies to determine factors predictive of weight gain and weight gain prevention. Such studies should emphasize populations disproportionately affected by obesity, include both genders, and encompass individuals at different life stages across the lifespan.

Accelerated identification and understanding of genetic factors that influence risk for obesity may help guide research on and implementation of interventions for those most at risk. Different forms of obesity (“obesities”) may result in part from different underlying genetic variations interacting with the environment. Genetic factors may also contribute to an individual’s success in weight loss or weight maintenance. Further research may elucidate the contribution of genetics to differing propensities of individuals for gaining, losing, or maintaining weight. For example, genetic factors may contribute to basal metabolic rate (the rate at which the body expends energy at rest). Certain genetic variations result in greater appetite—that can, in turn, lead to increased eating behavior.

New insights may be also gained from further exploration of the potential for genetic factors to influence behavior in other ways as well, for example, through dietary preference, through a tendency for fidgeting (which can burn energy), or through a desire to engage in exercise. Eating disorders represent another facet of genetically-influenced behaviors. The results of genetic research may help in developing different lifestyle interventions that may be useful for different people. (Additionally, as will be discussed in a later section of this document on medical interventions, genes identified through such studies may also be useful for new drug development efforts.) Increased knowledge of the impact of genetic variation on body weight would have implications for tailoring more effective strategies targeted to individuals for prevention and treatment of obesity.

These areas of research will provide a firm scientific foundation for the development of innovative interventions to modify behavioral and environmental factors that contribute to obesity.

Goals

Short-term Goals

- ▶ Incorporate the evaluation of public comprehension and acceptance of public health recommendations in the areas of physical activity, diet and weight control, as well as the assessment of current weight control/weight loss practices into national and regional health surveys. Such evaluations could include the assessment of the literacy skills and knowledge level of populations for making informed health decisions, as well as their acceptance of public health recommendations.
- ▶ Establish periodic surveys of healthcare providers who treat children and adults to evaluate the providers' knowledge, attitudes, and behaviors related to weight control and obesity management in clinical practice. Surveys should also explore barriers to implementation of weight control efforts, as well as factors believed to enhance delivery of such services.
- ▶ Assess children's environments, such as the home, school, and other community settings, to determine barriers to increasing physical activity and receiving optimal nutrition.
- ▶ Assess parental knowledge of developmentally appropriate physical activity and nutrition in children, as well as knowledge and skill in implementing behavior change.
- ▶ Support analyses of existing data from the National Health and Nutrition Examination Survey (NHANES) and other relevant national health surveys to determine age, sex, and race/ethnicity specific estimates of physical activity, dietary intake, and body composition in the U.S. population, using best available methods.
- ▶ Assess neurobehavioral factors (such as food craving and sedentary behaviors) that may contribute to obesity or weight control and weight loss.

Intermediate-term Goals

- ▶ Identify the contributions of various sociocultural, economic, familial, environmental, and behavioral factors to obesity development and prevention in adults and children, and assess different environments, such as the home, child care, school, and other community settings, for specific barriers to increasing physical activity and optimizing nutrition.
- ▶ Evaluate the impact of advertising messages on dietary preferences, physical activity, and sedentary behaviors in children and adults.
- ▶ Understand how the built environment influences behaviors such as eating and engaging in physical activity, that in turn impact body weight and obesity.
- ▶ Use prospective observational studies to identify potentially modifiable behavioral and environmental determinants of excessive weight gain and obesity in children, adolescents, and young adults, and to identify critical periods for inappropriate weight gain.
- ▶ Identify behavioral and environmental factors that are associated with successful long-term weight gain prevention and weight loss in response to lifestyle or other therapeutic interventions.
- ▶ Determine ways to increase the percentage of overweight/obese individuals who demonstrate motivation to undertake efforts to make long-term changes in their diet and exercise behaviors.

Long-term Goals

- ▶ Determine frequency and population-specific risk of different physical and behavioral characteristics of obesity associated with identified genetic variants, including differing body composition, eating and physical activity behaviors, and obesity-linked health problems.
- ▶ Identify genes associated with increased or decreased risk for obesity in metabolically well-characterized populations of men and women from diverse racial and ethnic groups.
- ▶ Identify genetic variants that are associated with successful long-term weight loss in response to lifestyle interventions.
- ▶ Use prospective observational studies to identify patterns of weight gain over a lifetime in individuals.

Research Topic

Designing and testing potential interventions that could be applied in different settings for obesity prevention and treatment

Combating the escalating obesity epidemic will require the development and testing of a variety of new approaches for increasing physical activity, decreasing sedentary behaviors, and improving diet. Obesity affects children, adolescents, and adults; individuals of different genetic backgrounds; people from a variety of cultures; and communities in different socioeconomic conditions. Thus, a range of behavioral and environmental approaches will be necessary to surmount the different challenges that individuals and communities may face in achieving and maintaining a healthy weight. Research should also evaluate whether gender or age differences exist in interventions designed to prevent and/or treat obesity. Although both prevention and treatment are discussed in this section, it is recognized that the

expertise and approaches necessary to develop interventions for primary prevention of obesity may differ substantially from those required for treatment once obesity has been established. Likewise, the interventions that are effective for obesity prevention may differ from those that are effective for treatment. Thus, inclusion of investigators with skills and knowledge in community-based prevention strategies, as well as those with expertise in weight management, will be required to develop comprehensive strategies for obesity prevention and treatment.

With respect to community-based efforts, research will benefit from the exploration of a variety of potential study sites, including community-based organizations such as youth service and faith-based organizations. It will also be valuable to explore potential community-based prevention and treatment strategies that are culturally-appropriate and target diverse population groups.

An example of the difficulties experienced by those who seek to lose weight can be drawn from the NIH-sponsored Diabetes Prevention Program (DPP) clinical trial, which tested strategies to prevent type 2 diabetes in high-risk individuals. Although the DPP demonstrated dramatic health benefits from modest changes in diet and physical activity, these modest lifestyle changes required intensive individualized behavioral intervention. Furthermore, following an initial weight loss of about 7 percent of body weight in the first year of the study, the participants began to regain some of the lost weight in subsequent years. Thus, increased research on approaches to behavior change, including motivational strategies to promote weight loss and maintenance, along with studies to investigate environmental approaches to obesity prevention, are critically important.

Enhanced study of diet will help inform lifestyle intervention strategies. This research would include, for example, investigations of the effects of different types of dietary components (macronutrient and micronutrient composition), such as the amount and type of fats, carbohydrates, and proteins in a diet. Further study will also be useful to explore the effects of dietary patterns, including the overall components of meals consumed in the home or restaurants. Knowledge gained from such research will help lay a foundation for science-based advice that connects to the cultural, linguistic, and communicative practices of diverse audiences.

Similarly, research is needed on the effects of different types, amounts, and frequency of physical activity to inform the development of lifestyle interventions. Although any successful campaign to achieve healthy weight must include a physical activity component, there are many factors important in research looking at the effects of exercise on weight gain and loss. Success may depend on identifying behavioral and lifestyle influences on compliance with an exercise regimen, especially among obese people. It will be necessary to optimize exercise parameters such as duration, frequency, and type of exercise, in order to identify the most effective means to increase energy expenditure. These may differ between obese and lean people; for example, those who are lean may be less prone to injury during weight-bearing exercise. Outcome measures, such as maximum oxygen consumption, maximum and absolute work intensity, anaerobic threshold, fat free mass, etc., should be carefully defined so they will accurately reflect physiological variables throughout a period of changing weight. Careful studies would define whether there are differences among obese and lean people in endocrine and neuroendocrine changes, and in the

metabolic changes accompanying exercise. It is also important to investigate whether weight loss due to increased activity is the same as weight loss due to dieting. As examples, there may be differences in post-weight loss metabolic efficiency, or different fat depots may lose mass differentially with the two interventions.

Different weight loss strategies may have different effects on biological processes in the body and on emotions and other psychological factors that may contribute to weight regain. Disordered eating patterns, such as binge eating, may also contribute to inappropriate weight gain, as well as difficulties with weight loss or weight maintenance.

Research efforts undertaken in these areas may not only lead to the design of new approaches to maintenance of a healthy weight after weight loss, but may also help refine interventions aimed at the initial weight loss. (Genetic research is described further in the section on medical approaches to preventing and treating obesity.)

Opportunities for research relevant to environmental modifications also come from “natural experiments” including, for example, studies of the efficacy of proposed policy changes in schools concerning food offerings and/or physical activity. The NIH must be poised to take advantage of these research opportunities as they occur. Rapid response mechanisms that have been used in such areas as emerging infectious diseases may be adaptable to allow NIH funded investigators to evaluate the effects of the changing environment in the real world. Such data may well provide a foundation for rigorous controlled studies to prevent or treat obesity.

Goals

Short-term Goals

- ▶ Identify potential approaches to modifying environments and policies to support increased physical activity, decreased sedentary behaviors, improved dietary quality and appropriate portion size, and prevention of inappropriate weight gain in children and adults.
- ▶ Explore the role of poverty, including food insecurity (limited access to safe, nutritious food) and lack of access to safe and convenient opportunities for physical activity, in the disproportionate prevalence of obesity in persons of low socioeconomic status.

Intermediate-term Goals

- ▶ Develop and test strategies to maintain healthy weight in children and adults through individual, interpersonal, and population-based interventions, in different settings, designed to increase physical activity, decrease sedentary behaviors, and improve diet. Evaluate the impact of the intensity of the interventions on the efficacy of such strategies.
- ▶ Evaluate the impact of factors such as parenting behaviors and familial environment on the etiology of overweight in childhood.

- ▶ Compare the effects of different physical activities—which vary by intensity, frequency, duration, and type—on appetite, energy expenditure, body fat distribution, fitness, weight loss, weight maintenance, mood, and other factors relevant to obesity and health.
- ▶ Develop and test potentially cost-effective approaches to the treatment of obesity, such as self-help groups, the Internet, cable television, or telemedicine.
- ▶ Elucidate the role of dietary macronutrient and micronutrient composition on energy metabolism, brain regulatory and brain reward pathways, appetite, and body composition in animal models.
- ▶ Evaluate the efficacy and sustainability of small changes in energy intake or physical activity on control of body weight.
- ▶ Elucidate factors involved in the development of individual food preferences and preference for active versus sedentary leisure pursuits, including stability of traits over time and potential strategies for modification of such preferences.
- ▶ Determine the relationship between mental disorders and obesity or the ability to achieve and maintain a healthy weight.
- ▶ Determine the impact of strategies that simultaneously address the prevention of eating disorders as well as obesity.
- ▶ Evaluate economic factors of interventions, including cost-benefit issues.

Long-term Goals

- ▶ Use weight loss models, such as diet, physical activity, drugs, and surgery, to understand the biological and psychological factors contributing to weight regain in humans.
- ▶ Elucidate the role of dietary macronutrient and micronutrient composition in energy metabolism, brain regulatory and brain reward pathways, appetite, and body composition in humans.

Long-term Overarching Goal

- ▶ **Evaluate the effectiveness of strategies designed to achieve and maintain a healthy weight in diverse populations of children and adults through interventions designed to i) promote individual behaviors that will increase physical activity and improve diet and ii) modify environments such as the home, school, workplace or other community settings to make them more conducive to widespread adoption of more healthful eating and physical activity behaviors. To facilitate the translation of scientific research into public health improvements, assure that clear and appropriate communication, including messages and information, about successful healthy eating, physical activity, and weight control strategies reaches diverse audiences. Additionally, inform healthcare providers and others about unsuccessful weight-loss strategies and communication efforts.**

Strategies and Opportunities for Achieving the Goals

This section addresses research efforts related to preventing and treating obesity through lifestyle-based approaches. The NIH supports investigator-initiated research projects and initiates research efforts through solicitations for grant applications and contract proposals. Investigator-initiated research represents a substantial portion of the funded portfolio, and the NIH will continue vigorous support of these efforts. As noted earlier, the Strategic Plan is focused on NIH-initiated efforts, which are developed in consultation with the external scientific and lay communities. These efforts complement the research projects initiated by investigators in several ways, for example, by encouraging further studies in areas of particular scientific opportunity or interest and in fields in which there are gaps in knowledge or particular barriers to be overcome.

Ongoing Efforts

Descriptions of ongoing efforts are presented in Appendix B.

Plans under Development

Diet composition and energy balance: The design of improved strategies to prevent or reduce overweight and obesity will benefit from further research on how different aspects of foods affect the body. For example, different effects might be observed with diets that vary with respect to: the amount and types of fats, carbohydrates, and proteins they contain; energy density; nutrient absorption; dietary patterns, or dietary variety. Fruit and vegetable consumption

may also play a role in energy balance. Diet composition may impact appetite, energy expenditure, weight loss, fitness, physical activity, where fat is located in the body (body fat distribution), blood glucose levels, or other factors relevant to overweight, obesity, and health. In addition to supporting studies on diet composition (described in Appendix B), the NIH plans to further strengthen research in these areas.

Long-term weight maintenance—basic and clinical studies: Although there are many well-accepted methods to reduce initial body weight by 7 to 10 percent, long-term maintenance of that lost weight is more difficult. Yet, weight loss maintenance is critical in preventing the complications of overweight and obesity. Thus, the development and assessment of successful interventions will require pursuing a variety of research avenues with respect to long-term weight maintenance. In addition to supporting a clinical trial to test specific interventions on weight loss maintenance (described in Appendix B), the NIH will also encourage studies to elucidate the molecular and behavioral mechanisms underlying weight regain after intentional weight loss, and to examine appetite, energy expenditure, and other factors during weight maintenance and regain periods across the lifespan.

Mechanisms of physical activity behavior change: The NIH will encourage research to elucidate the psychosocial, environmental, and physiological factors involved in the mechanisms of behavior change with respect to physical activity to better understand the factors involved in its causal pathways. This research would increase the knowledge base necessary to develop effective physical activity interventions in children, adolescents, adults, and older adults.

School-based interventions relevant to childhood obesity: NIH efforts are being developed to expand research in the area of school-based interventions to prevent obesity in children and adolescents. Because an alarming increase in type 2 diabetes in children is thought to be driven by obesity and physical inactivity, the scope of school-based interventions to be supported is expected to encompass research that strives to prevent “pre-diabetes,” a condition in which blood glucose levels are higher than normal, but are not yet diabetic.

The National Children's Study (NCS): This study is being planned to examine the complex relationship between health and the environment for approximately 100,000 U.S. children and their families. Enrollment would begin before birth and follow up would continue for at least 21 years. The planning for the NCS involves the collaborative efforts of the NIH, the Centers for Disease Control and Prevention, the U.S. Environmental Protection Agency, and other Federal agencies. The authorizing legislation for this study, Title X of the Children's Health Act of 2000, calls for a broad and deep investigation of the multitude of factors potentially associated with all aspects of child health and development. There is substantial public health concern about the impact of the quality of the environment on child health and development but surprisingly little research to help policy makers determine which environmental factors are harmful, harmless or helpful. Obesity and physical development have been identified as one of five priorities for the NCS to examine. The NCS will likely have sufficient statistical power to examine disorders of physical development related to diabetes, obesity and altered puberty. The longitudinal nature of the data and the ability to examine the interaction of multiple environmental factors with an individual's genetic composition are expected not only to provide insights into growth-related disorders, but also to provide a strong study of variations in growth, and

physical and reproductive development that may be affected by the environment. It is planned that obesity and physical development would be studied in relationship to five priority exposures: physical environment, chemical exposures, biologic environment, genetics and psychosocial milieu.

Testing worksite interventions: Through a program on Overweight and Obesity Control at Worksites, the NIH will encourage the development of new studies to test interventions that are innovative and emphasize environmental approaches or a combination of environmental and individual approaches at worksites to promote weight control in adults. The purpose is to support studies designed to determine whether worksite interventions that include environmental strategies are successful in preventing, controlling, or treating obesity. Environmental strategies include programs, policies, or organizational practices to influence health behaviors by, for example, increasing the availability of, and providing access to, healthful food choices and facilities for physical activity and creating a socially supportive climate.

*Undercontrolled and addictive behaviors—
developing a translational research agenda:*

Although most obese persons do not report binge eating or compulsive overeating, a substantial minority do report such difficulties. The NIH is planning a workshop that will explore the commonalities between obesity and other undercontrolled and addictive behaviors. Particular emphasis will be placed on neural systems mediating metabolic and motivational processes involved in energy regulation, as well as genetic and environmental influences on neural systems involved in energy homeostasis. Interactions of neural networks mediating cognitive and emotional processes with hypothalamic structures affecting energy balance will be presented. The commonalities of brain mechanisms underlying food and drug cravings will be explored using brain imaging. Brain imaging studies

also will be discussed to determine similarities in neurobiological processes involved in both pathological overeating and drug-taking behavior, as well as to reveal divergence in brain mechanisms involved in adaptive versus nonadaptive behaviors.

Transdisciplinary Research on Energetics and Cancer:

The NIH will support the establishment of centers in nutrition, energetics, and physical activity and cancer outcomes. These centers will involve scientists from multiple disciplines; and encompass projects spanning the biology and genetics of energy balance to behavioral, socio-cultural, and environmental influences upon nutrition, physical activity, weight, energy balance, and energetics. The centers will focus on two great challenges in the area of energetics and cancer: 1) Enhancing the understanding of the mechanisms underlying the association between energy balance and carcinogenesis across the cancer continuum from causation and prevention through survival, and 2) Developing effective innovative approaches with broad population impact at the social-environmental and policy level for prevention of obesity. The latter will focus on children and on critical time periods among adults during which weight gain is likely to occur, such as with smoking cessation, cancer treatment, and major life transitions involving work or family.

Provider surveys: As in many areas of health, physicians and health professionals have the potential to play a critical role in the prevention and treatment of obesity. The NIH is examining the potential for developing periodic surveys of providers to examine knowledge, attitudes, practices and barriers related to addressing obesity prevention and treatment in clinical practice. Results from these surveys can be used to identify key targets for interventions to improve clinical practice.

Economics: Societal values, market and economic forces have an enormous impact on diet, physical activity, and weight control practices. In addition, obesity and related diseases and disorders are contributing increasingly to healthcare costs. The NIH will encourage economic research on diet, activity, and energy balance in at-risk populations. The NIH would encourage research on the development of innovative economic methods, the identification, evaluation and development of new data sources and applied research that would provide useful input for the design of public education and intervention programs and policies.

Prevention and treatment of pediatric obesity in primary care settings: The primary care setting, such as a pediatrician's or family physician's office, may provide a powerful venue for interventions to prevent and/or treat childhood obesity. To capitalize on this opportunity to address the rising prevalence of childhood obesity, the NIH plans to bolster research on the development and testing of primary care office-based programs for efficacy in accomplishing weight loss in overweight children and in preventing excessive weight gain in children at risk for overweight because of their current body mass index (BMI), trajectory of weight gain, race, ethnicity, family history of overweight or type 2 diabetes, and/or mother's glycemic status during pregnancy.

Concepts for Future Research

Site-specific approaches to prevention and treatment of pediatric obesity: To complement a new effort to advance research on prevention and treatment of childhood obesity in primary care settings, the NIH recently held a workshop to assist in the development of another new effort that would encourage research on methods for preventing and treating pediatric obesity in various other site-specific settings, such as,

for example, the family/home, day-care or pre-school, school, or other appropriate community venues. The objective would be to explore methods in pediatric populations for the primary prevention of inappropriate weight gain among those not overweight, secondary prevention to prevent further weight gain among those already overweight or obese, or tertiary prevention, i.e., treatment of overweight or obesity to prevent the complications of associated health conditions.

The built environment and obesity: There is suggestive evidence that elements of the built environment, such as aspects of community design that hinder physical activity, may contribute to obesity. The NIH seeks to promote studies to identify and create instruments to measure the impact of healthful community environments on behavior and lifestyle choices. With the availability of such evaluative tools, the NIH will also strive to foster efforts to develop and assess new cost-effective prevention and intervention strategies that promote healthful environments and behaviors aimed toward reducing obesity. This research effort will benefit from integrated, multidisciplinary research teams, including, for example, biomedical scientists, behavioral scientists, social scientists, clinicians, epidemiologists, planners, developers, architects, and community members. This area of research would likely help to inform public policy setting relevant to obesity.

Neurobiology of motivational and other processes—insights into obesity: Researchers are revealing overlaps in human brain systems that mediate both food and drug reward. Studies of addictive, excessive and compulsive behaviors may shed new light on obesity and will have important implications for its treatment. Other brain imaging research has shown that obese individuals have higher metabolic activity in brain areas subserving sensation to the mouth, lips, and tongue, and thus the enhanced activity in

these regions involved in the sensation of food could make food more palatable and rewarding in obese individuals. To build on these findings, the NIH plans to develop initiatives for encouraging investigator-initiated research in areas related to the neurobiology of motivational processes that underlie a variety of behaviors associated with food consumption. These studies will provide novel insights into the study of obesity and into the understanding of eating disorders generally.

Research resource on obesity, diet, and physical activity related policies and legislation: Tobacco policies, such as smoking laws in public areas, have had a tremendous impact on smoking behavior at the population level. Health related and non-health related policies may also be important in regulating physical activity and dietary behaviors at the population level. Such policies include issues such as school related policies regarding physical activity, food products provided in vending machines, school lunch and day care, urban planning related to the built environment to facilitate physical activity, and health-care coverage for services related to weight control, physical activity, and diet. The NIH has initiated pilot efforts to develop a research resource related to tracking legislation and policies influencing diet, physical activity, and weight control practices. This research resource will be made available to investigators to analyze the impact of these factors on diet, physical activity and weight-control practices at the population level and within clinical practice. As such, this effort will complement and expand upon efforts of the Centers for Disease Control and Prevention (CDC) in this area. The NIH is coordinating with other Federal and non-Federal organizations in developing this research resource, including the CDC and the Robert Wood Johnson Foundation, which are also supporting related efforts.

SCIENTIFIC THEME:

Preventing and Treating Obesity Through Pharmacologic, Surgical, or Other Medical Approaches

Research Topic

Discovering and building understanding of the molecules and biological pathways that regulate appetite, energy expenditure, and the storage of energy as fat

To complement and enhance research on lifestyle strategies for preventing obesity, the NIH plans to build upon research that is elucidating the roles of an array of molecules and biological signaling pathways that control energy balance. Included among these molecules are hormones and other factors that regulate appetite, the storage of excess calories as fat, and energy expenditure. These molecules, which are produced by the brain, gut, fat cells, or other organs, are part of an elaborate network of signaling pathways connecting many parts of the body, including a region of the brain called the hypothalamus, to achieve an integrated control of metabolism. Additionally, when they reach their destination, these molecules also set off a cascade of signals—carried by additional sets of biological molecules—within individual cells to direct the cells to perform various tasks. As obesity develops, the same regulatory systems that maintain exquisite balance between energy intake and energy expenditure adjust to defend vigorously the higher weight, thus resisting an obese individual's attempts to lose weight and keep off the pounds. Fundamental research on hormones produced by the gut, fat cells, and other organs and tissues is also beginning to offer tantalizing hypotheses, at the molecular level, as to how the body's innate regulatory systems may make weight loss and maintenance of lost weight so chal-

lenging. By providing new “targets” (molecules or the biological signaling pathways through which they act) for drug development, these lines of research could accelerate the development and evaluation of potential new treatment strategies. Drugs that home in on one of these targets could beneficially affect appetite, food absorption, energy expenditure, or body composition.

The formation of new neural connections between functionally related sets of neurons is a process that continues throughout adulthood. The ontogeny of the hypothalamic neural network that controls feeding behavior and an understanding of important humoral signals and environmental factors that might be critical for the formation of these pathways may be important for understanding the etiology of childhood obesity. Research focused on understanding the plasticity of these critical pathways and its impact on energy balance is needed. There is mounting evidence that nutritional and other environmental or maternal factors, when present during intrauterine or post-natal development, can strongly influence the subsequent development of obesity. Knowledge of both the developmental neurobiology of the regulatory networks involved in energy balance as well as the identification of environmental factors that can alter the development of this system is critical to prevention of obesity.

Bariatric surgery—some forms of which disrupt normal neural, gastrointestinal, and endocrine pathways—may also provide new insights into the role of peripheral signaling (signaling from various parts of the body to the control centers in the brain) in energy balance.

Genetic studies in animals and humans provide yet another avenue to the discovery of novel molecules or biological pathways linked to obesity, and continued genetic research may accelerate the development of therapeutic approaches, as well as confirm or refute the importance of previously-studied molecules in contributing to human obesity. Studies will also be important to evaluate gene-environment interactions that may be critical for affecting body weight. Additionally, genetic studies may well form the basis for selection of a particular treatment or preventive strategy tailored for optimal benefit for an individual patient or subpopulation.

A more comprehensive understanding of the body's regulation of energy balance—including new insights into molecular underpinnings of behavior—should continue to spark innovative ideas for therapies for weight loss and weight maintenance.

Goals

Short-term Goal

- ▶ Use model organisms (such as mice or other organisms) to identify novel pathways or molecules involved in regulation of body composition, food consumption, or physical activity levels.

Intermediate-term Goals

- ▶ Identify genes associated with increased or decreased risk for obesity in metabolically well-characterized populations of men and women from diverse racial and ethnic groups.

- ▶ Define the brain regulatory pathways that control food intake, energy expenditure, and energy storage, and identify the effects of caloric restriction and increased energy expenditure on energy metabolism, brain regulatory pathways, and body composition.
- ▶ Elucidate the roles of dietary macronutrient and micronutrient composition, physical activity, and fitness in energy metabolism, brain regulatory pathways, appetite, and body composition in animal models.
- ▶ Explore the potential role of drug therapy and bariatric surgery in the treatment of obesity in children and adolescents to determine the effectiveness, risks, and benefits of these treatments in pediatric populations.

Long-term Goals

- ▶ Elucidate the roles of dietary macronutrient and micronutrient composition, physical activity, and fitness in energy metabolism, brain regulatory pathways, appetite, and body composition in humans.
- ▶ Use weight loss models (e.g., diet, physical activity, drugs, and surgery) to understand the biological and behavioral factors contributing to weight regain in humans.
- ▶ Identify components of the central and peripheral nervous system that are influenced by nutrition, physical activity, and social and environmental factors to affect weight and body composition at critical periods throughout life such as the fetal period, neonatal period, adolescence, pregnancy, menopause, and older adulthood.

- ▶ Determine frequency and population-specific risk of different physical and behavioral characteristics of obesity (for example, differing body composition, eating and physical activity behaviors, and obesity-linked health problems) associated with identified genetic variants.
- ▶ Identify genetic variants that are associated with successful long-term weight loss in response to medical or surgical interventions.

Research Topic

Accelerating the design and testing of obesity prevention and treatment strategies

As described, the identification of molecules and signaling pathways that regulate energy balance is already influencing the design of strategies to develop new drugs to prevent or treat obesity. Not only can researchers funded by NIH generate new ideas for drug therapies based on this molecular research, but the pharmaceutical industry can also continue to use this scientific knowledge to screen for and test the safety and efficacy of potential new medical interventions. Enhanced understanding of the varied and complex causes of weight gain, at the molecular/genetic level, can lead to the generation of new therapies. A child's developmental stage (such as puberty) may impact energy regulation and the ability to maintain weight loss or slow the trajectory of weight gain, and could also influence the timing of effective prevention or treatment efforts.

In addition to facilitating the design of new interventions, further knowledge of the complex factors influencing obesity may also help clinicians to select interventions that are likely to be most effective, based on the underlying causes of a person's obesity (whether the interventions are focused on lifestyle

change or also encompass drugs or other medical strategies). A striking example of this concept is the treatment of a rare form of obesity caused by a deficiency in the hormone leptin, which is normally made by fat cells. Leptin travels from fat cells to signal the brain about body fat stores, and it also influences other biological processes relevant to body weight. For individuals who lack leptin, it would be extremely difficult to achieve weight loss through lifestyle interventions alone, and some drug therapies would be unlikely to work well if at all. However, replacing their missing hormone, leptin, through injections, is extremely effective not only in helping them lose weight, but also in reversing the other negative health consequences of this missing hormone. The fact that most people who are obese do not suffer from leptin deficiency—and, in fact, are leptin resistant—also highlights the importance of intensified molecular, genetic, and physiologic research to delve into the factors underlying more common forms of obesity, so as to accelerate the development and testing of a variety of potential new prevention and treatment strategies.

The extent to which weight reduction strategies for the treatment of obesity should include dietary supplements is a key area for future research. Protein, vitamin, and mineral nutrition are critical during weight reduction and maintenance. Dietary Reference Intakes for individuals must continue to be met even on reducing diets. The lower the diet is in calories, the greater the risk that intakes of essential nutrients will be low or inadequate. Essential dietary nutrients likely to be limiting in weight reduction diets include protein, potassium, magnesium, vitamin B6, iron, and calcium. Aside from nutrient adequacy, people use dietary supplements to enhance weight loss. Further research is required to elucidate the mechanisms of action of such supplements for this purpose because it is probable that different botanical supplements and bioactive food components will have different mechanisms. This research is needed to develop

scientifically sound evidence-based public health recommendations that are targeted for age, sex and physiological status. NIH research on dietary supplements will continue to provide important input for other Federal agencies, in the form of science-based evidence, useful in regulatory decisions and public health policy by the Food and Drug Administration and the Department of Health and Human Services, respectively.

Pharmacologic, surgical and other biological approaches would complement and could be used in combination with lifestyle-based interventions. It is important to understand how best to accomplish this integration. Lifestyle and pharmacologic approaches could be used in combination from the onset of treatment or could be applied in a sequential, stepped-care fashion. If medication is introduced sequentially, it is not known when and in whom it should be used (after a set time period or a set amount of weight loss or regain). Research is also needed to determine how best to combine lifestyle and surgical approaches to obesity.

Goal

Long-term Overarching Goal

- ▶ **To complement lifestyle interventions, use knowledge of regulation of food intake, energy storage, and energy expenditure to identify drug targets for development of novel medications, and to accelerate the development and evaluation of surgical techniques and other therapeutic technologies. To enhance efficacy of these therapies, while minimizing population risk, design strategies that target specific medical interventions to individuals most likely to benefit and who are at particular risk for obesity-associated health problems.**

Strategies and Opportunities for Achieving the Goals

This section addresses research efforts related to treating and preventing obesity through drug-based, surgical, or other medical approaches. These approaches would complement—and could be used in combination with—lifestyle-based interventions. The NIH supports investigator-initiated research projects and initiates research efforts through solicitations for grant applications and research contracts. Investigator-initiated research represents a substantial portion of the NIH funding portfolio, and the NIH will continue vigorous support of these efforts. As noted earlier, the Strategic Plan is focused on NIH-initiated efforts, which are developed in consultation

with the external scientific and lay communities. These efforts complement the research projects initiated by investigators in several ways, for example, by encouraging further studies in areas of particular scientific opportunity or interest and in fields in which there are gaps in knowledge or particular barriers to be overcome.

Ongoing Efforts

Descriptions of ongoing efforts are presented in Appendix B.

Plans under Development

Integrative approaches to understanding energy balance: Multidisciplinary, large-scale studies will be useful for understanding the interconnections among numerous and diverse biological pathways that affect energy balance. For example, studies are revealing the complex energy-balance regulatory pathways coordinated within a region of the brain called the hypothalamus, which receives signals from a variety of hormones. The brain also receives other types of signals, from throughout the body and from the environment, that may also affect energy balance. Additionally, increasing evidence points to the role of perturbations in the body's production, storage, or burning of fat in the development of health problems, but the exact mechanisms by which health problems arise remain unclear. Thus, the NIH will seek ways to enhance understanding of how all of these factors interact so as to assemble an integrated picture of their inter-related effects on obesity and health.

Genetic research in model organisms: Research in numerous different types of laboratory mice (mouse models) has provided a wealth of knowledge relevant to human biology and disease, and studies of other organisms are also yielding valuable information. The NIH will be encouraging new genetic studies of obesity-related traits in "model organisms" in which techniques for gene discovery are much more powerful than in humans. The human counterparts of genes found through this research could subsequently be identified and tested for association with obesity in humans.

Environmental effects on the development of molecular pathways that control energy balance: Environmental factors, such as inadequate nutrition or the presence of diabetes in a mother during preg-

nancy, as well as inadequate nutrition during the neonatal period, are associated with overweight and obesity in the offspring. Additionally, there is evidence that during certain critical periods of fetal or early childhood development, environmental factors may affect the formation of molecular pathways in the brain that regulate energy balance. These environmental factors may potentially include, for example, caloric intake or the types of foods in the diet. The NIH is planning to encourage further research in animals to help clarify the effects on overweight and obesity of environmental factors present during development. This research may lead to the design of new strategies to improve the health of mothers and their offspring.

Role of lipids in the pathogenesis of obesity: Lipids, which include different types of fatty acids, cholesterol, and other molecules, have important biological roles in the body, but they can also contribute to adverse health conditions when not properly regulated. The NIH recently convened a meeting to address the underlying molecular mechanisms associated with the role of lipids in the development of obesity and its associated diseases, such as cardiovascular disease and type 2 diabetes. The results of this workshop are being considered and will help guide future research plans in this area.

Role of antipsychotic and mood stabilizing medications: Antipsychotics and mood stabilizing medications have a side effect of weight gain for many with mental illness. The NIH will strive to understand the causes of this weight gain and to develop strategies that can be used to prevent or mitigate excessive weight gain. This research ultimately may provide strategies to ameliorate this adverse effect of current medications, and may provide a scientific basis for the development of new medications that lack this side effect.

Concepts for Future Research

Neurobiological basis of obesity: Current models do not reflect the quantity and diversity of input pathways that modulate the control of eating behavior in humans. Both methods and models are needed that can define the interactions between diverse input signals such as sensory cues (for example, smell, taste, and sight), endocrine signals (such as insulin, leptin, glucocorticoids, and ghrelin), nutrient signals (glucose, cholesterol, free fatty acids) and neural signals transmitted through the brainstem. A novel effort would support collaborative programs focusing on understanding the biological basis of human eating behavior with a goal of developing better strategies for the prevention of obesity. A primary objective of this effort would be to bridge the gap between understanding at the molecular and genetic level of neural pathways involved in food intake and the understanding of behavioral influences on human obesity. The complex interactions between human biology, behavior, and environment, which are critical to the understanding of the underlying molecular mechanisms and prevention of obesity, will require expertise and technical approaches not generally found in a single laboratory or investigative team.

Genetics and genomics of human obesity and its associated health conditions: Because of the genetic complexity of obesity, the search for predisposing genes has proven to be extremely challenging. Based on input from a recent NIH-sponsored workshop and from other sources, the NIH is considering new ways to facilitate and accelerate the identification of genes and gene-environment interactions that confer susceptibility to obesity in humans. In addition to studies to identify genes that predispose a person to becoming obese, this research concept also encompasses studies to understand genetic variation that would explain why some obese individuals develop serious associated diseases while other obese individuals do not. (Research focused on the diseases associated with obesity is covered extensively in the following section.) In addition, identification of genes that contribute to constitutional thinness in our increasingly obesogenic environment may also assist with identifying pathways that may be protective against the development of obesity. Efforts to identify new pathways or proteins as targets for drug discovery will require complementary studies in model organisms with confirmatory studies in humans. Recent progress in such diverse organisms as worms and fruit flies suggests that this approach can deliver a new pipeline of drug targets.

SCIENTIFIC THEME:

Breaking the Link Between Obesity and Its Associated Health Conditions

Research Topic

Discovering biomarkers — molecular signs — and other molecular factors that may serve as harbingers of the development of associated health problems in individuals who are obese

The health problems fueled by obesity are complex and deadly. Obesity is a strong risk factor for type 2 diabetes, heart disease, hypertension (high blood pressure), and stroke. Type 2 diabetes itself leads to numerous additional health problems, including heart disease, the leading cause of diabetes-related deaths; end-stage kidney disease, which requires dialysis or a kidney transplant to sustain life; blindness; nervous system damage that can contribute to a need for lower-extremity amputations; and other serious complications. Obesity is also considered a driving force of the metabolic syndrome in children and adults. The metabolic syndrome, also known as Syndrome X or insulin resistance syndrome, is a constellation of medical problems that puts people at increased risk for cardiovascular disease and for type 2 diabetes (13). A recent report also noted an alarming prevalence of the metabolic syndrome in adolescents (14). Obesity is strongly linked to common forms of cancer including colon, endometrial, esophageal, renal cell, and post-menopausal breast cancer. It also contributes to poorer prognosis for some cancers, such as breast cancer (15). Recently, obesity has been associated with more

aggressive prostate cancer at diagnosis and higher recurrence rates after patients undergo surgery to remove the entire prostate. This finding also suggests the value of further research to explore potential associations between obesity and stage-at-diagnosis for other cancers. Additional health conditions associated with obesity include sleep apnea, asthma, osteoarthritis, urinary incontinence, non-alcoholic fatty liver disease, gallbladder disease, thromboembolic disease (blood clots in the legs and lungs), and psychiatric disorders such as depression and eating disorders. Enhanced research efforts will be important to increase understanding of how obesity progresses to these associated health conditions, and of how to break these links. Conversely, research efforts will also be valuable in elucidating how certain medical conditions may contribute to obesity.

Not all overweight and obese people develop these related health problems. Thus, new research efforts to identify biological “markers” (or “biomarkers”) associated with disease risk will be important. These biomarkers may be certain molecules or patterns of molecules found in obese individuals, physical characteristics of fat or fat tissue, or other traits. Such research may lead to the development of novel prevention or treatment strategies. Additionally, studies in this area will help to identify overweight or obese individuals at particular risk for certain associated health conditions; these individuals may particularly benefit from prevention or treatment interventions.

Goals

Short-term Goals

- ▶ Establish guidelines for collection of data and samples that would encourage the assessment of multiple obesity-associated health conditions within diverse populations.
- ▶ Identify novel biomarkers that are associated with obesity-associated health conditions using genomic or proteomic approaches across diverse racial and ethnic groups.

Intermediate-term Goals

- ▶ Determine the relationship between obesity and inflammatory markers, other biomarkers, and such other factors as cardiorespiratory fitness, that influence the development and progression of multiple medical conditions and overall health status.
- ▶ In well-characterized clinical trial populations, test the utility of novel biomarkers to predict the progression of health conditions associated with obesity, or to predict the efficacy of therapeutic approaches for preventing or treating obesity or its associated health conditions.

Long-term Goals

- ▶ Identify genetic variants that affect risk of development of obesity-associated health conditions, and determine their incidence, prevalence, and relative risk in diverse populations.
- ▶ Use biomarkers to optimize individual therapeutic approaches.

- ▶ In children and adolescents, determine markers for the development of obesity-related diseases, across the continuums of both development and degree of overweight, that would provide indicators for early intervention.

Research Topic

Designing and testing potential strategies to block the development of obesity-associated health conditions

Interventions that promote weight loss can simultaneously reduce the risk of serious health conditions associated with obesity, such as type 2 diabetes in high-risk individuals. It will also be important to evaluate the impact of prevention of further weight gain on health outcomes in overweight or obese individuals. By capitalizing on new efforts to build knowledge of how obesity is associated with various health conditions, it may also be possible to develop novel approaches for breaking the link between obesity and an associated disease or other health condition, even in the absence of weight loss. Some studies have suggested that intentional weight loss may, in certain instances, also have adverse effects such as gallstone formation and bone loss. Thus, as a corollary to pursuing research to break the link between obesity and its associated health conditions, further exploration of any potential negative effects of losing weight will also be important to help reduce the risk for possible medical problems associated with weight loss. Studies that include sub-populations based on gender, race, or ethnicity will be valuable. In addition, recent studies suggest that obese individuals are less likely than those of normal weight to receive general preventive healthcare, such as pap smears. The factors associated with this differential use of preventive healthcare practices remain to be

elucidated. Also related to research on medical conditions associated with obesity would be new efforts to evaluate the impact of messages about weight loss on psychosocial functioning, including the minimization of stigma, promotion of positive body image, and prevention of eating disorders in susceptible individuals. Thus, it would be valuable to assess, in this context, the psychological impacts of public health messages or campaigns to prevent or reduce obesity.

Goals

Intermediate-term Goals

- ▶ Determine the long-term individual and combined effects of diet, physical activity, and overall energy expenditure on body composition and obesity-associated health risk independent of weight change.
- ▶ Use animal models to determine whether sustained weight reduction after obesity has developed affects morbidity and mortality.
- ▶ Determine how mood disorders, eating disorders, and adverse childhood experiences may be related to the development of obesity or the ability to achieve and maintain a healthy weight.
- ▶ Study the potential impact of weight loss interventions or obesity prevention campaigns on the development of eating disorders and on stigma and/or discrimination.

- ▶ Determine whether different approaches to weight loss—including lifestyle interventions, pharmacologic therapy, and surgery—produce comparable improvements in health, and whether these improvements are related to the magnitude of weight loss or independent effects of the medication, surgery, diet, or physical activity.
- ▶ Determine factors associated with decreased preventive healthcare utilization in obese individuals, and assess strategies to improve access to and utilization of preventive and other healthcare services in obese individuals.

Long-term Goal

- ▶ Identify aspects of differential fat distribution or longitudinal patterns of weight change that are associated with greatest health risk in diverse populations.

Long-term Overarching Goal

- ▶ **Use knowledge of mechanisms whereby obesity increases risk for serious diseases and disorders to enhance the efficacy of weight loss in preventing or improving obesity-related health conditions. Additionally, develop potential therapeutic approaches for ameliorating these conditions independent of weight loss, for example, by improving fitness. Further, identify and develop weight loss strategies that reduce potential adverse effects of weight loss.**

Strategies and Opportunities for Achieving the Goals

This section addresses research efforts related to the link between obesity and its associated health problems. The NIH supports investigator-initiated research projects and initiates research efforts through solicitations for grant applications and research contracts. Investigator-initiated research represents a substantial portion of the NIH funding portfolio, and the NIH will continue vigorous support of these efforts. As noted earlier, the Strategic Plan is focused on NIH-initiated efforts, which are developed in consultation with the external scientific and lay communities. These efforts complement the research projects initiated by investigators in several ways, for example, by encouraging further studies in areas of particular scientific opportunity or interest, or in fields in which there are gaps in knowledge or particular barriers to be overcome.

Ongoing Efforts

Descriptions of ongoing efforts are presented in Appendix B.

Plans under Development

Using proteomics technology to search for biomarkers for health conditions associated with obesity: Just as large-scale research into the expression of genes in a cell or tissue, or “genomics,” is revolutionizing biology, large-scale research to identify and obtain a comprehensive understanding of the proteins in cells, tissues, and body fluids, and how they function together—“proteomics”—could also provide unique insights into diseases. The NIH plans to foster the application of proteomics techniques to obesity as a potential way of identifying biomarkers associated with obesity-related health conditions.

Heterogeneity of fat tissues in different parts of the body: Fat tissue in different parts of the body appears to have different properties. For example, although the total amount of fat in the body is relevant to health, visceral fat (fat surrounding the internal organs in the abdomen), rather than total body fat, appears to be the better predictor of obesity-associated health conditions. The NIH will seek to intensify studies to better understand the differences between fat tissues (“fat depots”) in different locations, and to identify biological molecules that may mark different fat depots. It is hoped that enhanced research in this area would yield new targets for therapeutics to disrupt the link between obesity and its associated health conditions. While different depots of fat are clearly linked to different levels of obesity-associated morbidity, understanding this link will require more research on functional differences in these depots, not just identification of biomarkers. Expanded research on regulation of metabolically active tissues in humans will provide a basis for targeted therapeutic development. Identification of key determinants of shifting fat storage from adipose tissue to organs such as liver and muscle will likely be critical to discovering the links between obesity and associated health conditions.

Transdisciplinary Research on Energetics and Cancer: As noted, the NIH will support the establishment of centers in nutrition, energetics, and physical activity and cancer outcomes. These centers will involve scientists from multiple disciplines, and encompass projects spanning the biology and genetics of energy balance to behavioral, socio-cultural, and environmental influences upon nutrition, physical activity, weight, energy balance, and energetics. The centers will focus on two great challenges in the area of energetics and cancer: 1) Enhancing the understanding of the mechanisms underlying the association

between energy balance and carcinogenesis across the cancer continuum from causation and prevention through survival, and 2) Developing effective innovative approaches with broad population impact at the social-environmental and policy level for prevention of obesity. The latter will focus on children and on critical time periods among adults during which weight gain is likely to occur, such as with smoking cessation, cancer treatment, and major life transitions involving work or family.

Ancillary studies of energy balance and cancer-related exploration in human studies: Epidemiologic and intervention research within human populations can provide essential self-report and objective measures about diet, anthropometry and physical activity which may be key to defining potential mechanisms by which energy balance, flux, body composition and related factors influence cancer risk and prognosis. In addition, examination of associations of these measures with biologic specimens such as blood, urine, exfoliated cells, and/or tissues can afford opportunities to study underlying metabolic and genetic etiologic mechanisms in relation to energy balance and cancer. The NIH plans to support new research based on data collected in existing studies; this research would expand efforts to explore these factors by supporting exploration of new hypotheses with existing data and supporting the collection and analyses of additional measures and biological samples when needed. At least three types or levels of additional research could be supported within existing studies:

- 1) Testing new hypotheses with existing data,
- 2) Performing additional assays on existing biologic specimens to examine new hypotheses, and
- 3) Collection and analyses of additional self-report or objective measures of diet, anthropometry and physical activity, and/or biological specimens.

SCIENTIFIC THEME:

Cross-cutting Topics

Research Topic

Health Disparities—Addressing the needs of specific populations

An integral aspect of the obesity research planning process is addressing the special needs of specific populations affected by obesity, as noted earlier in the section on Health Disparities. Children constitute one such population: obesity is not only rising at an alarming rate in children, but also, by occurring at such an early age, obesity in these individuals may lead to a lifetime of serious health problems. A number of racial/ethnic minorities are disproportionately affected by obesity, including African Americans, Hispanics, and American Indians; children of these groups are particularly affected. Socioeconomic status is also related to obesity, which is more prevalent among those who are poor. There may be sex/gender differences not only in the development of obesity, but also in responses to interventions; gender-specific factors such as pregnancy and menopause may also contribute to health risks associated with obesity. The impact of obesity on older adults is also an area important for further study. Disability may be associated with obesity both as a contributing risk factor and as a consequence. Finally, those who are extremely obese are at particularly heightened risk for obesity-associated health problems and decreased quality of life.

Goals addressing particular research needs relevant to these populations are found throughout the Plan, and many other goals in the Plan reflect broad areas that encompass research on all populations. Yet, recognizing the critical importance of research in this area, the following goal is set forth as a guiding principle for obesity research planning.

Goal

- ▶ In developing new initiatives or programs for research or education/outreach campaigns, special emphasis should be given to addressing the diverse needs of populations disproportionately affected by obesity, including children, racial/ethnic minorities, women, older adults, persons of lower socioeconomic status or low literacy, those with disabilities, and individuals with extreme obesity.

Research Topic

Enhancing research resources and multidisciplinary and interdisciplinary research teams

Numerous ongoing and planned research efforts could not have been imagined years ago. The fruits of past research investments include scientific discoveries in such fields as the molecular regulation of appetite and energy expenditure, regulation of fat cells, and technologies that facilitate advanced research efforts. To continue to bolster research progress, many planning efforts are directed to developing and strengthening resources that would enable cutting-edge research. Such efforts may include encouraging the invention or refinement of enabling technologies, such as new imaging techniques or novel methods for measuring energy expended at rest and during physical activity or food intake, as well as identifying existing valuable resources that may be limiting and addressing their availability to investigators. There is also a need for very accurate measurements of energy intake and expenditure to address quantitative aspects of the subtle imbalance in energy that contributes to obesity. Research would also benefit from improved instrumentation to measure body

composition in individuals who are severely obese. Further research relevant to the measure of energy efficiency may help increase understanding of why some people may gain—or lose—weight more readily than others. Another valuable resource would be a set of biomarkers associated with the adverse health effects of obesity. Such markers may, for example, help in the diagnosis of obese individuals at particular risk for obesity-associated health conditions, and may also serve as useful tools in the evaluation of potential therapeutic approaches for obesity or for its associated health conditions.

Other types of resources with applicability to multiple fields of endeavor include, for example, emerging technologies such as metabolomics (the study of the complete set of metabolites—small molecules such as lipids and amino acids—in cells, tissues, organs, and body fluids), and e-health applications and tools that could effectively help consumers and patients understand their health, identify necessary behavior changes, and make informed decisions. Such resources also include genetic analyses and animal models relevant to different aspects of obesity, as addressed previously.

In addition to material research resources, the fostering of multidisciplinary and interdisciplinary teams of investigators will help catalyze new efforts in obesity research. Researchers with expertise in numerous disciplines can offer important contributions to obesity research. These include, for example, molecular biologists, biochemists, geneticists, physiologists, behavioral scientists, social scientists, and clinicians with expertise in such specialties as internal medicine, pediatrics, and surgery. For example, a multidisciplinary team may include researchers from fundamental disciplines, with expertise in studying the molecular and other mechanisms underlying weight gain, collaborating with clinical researchers who work with patients in clinical trials. Finally, of major importance is support for research training in disciplines relevant

to obesity, including nutrition, physical activity, and other fields. Such training activities would include efforts focusing on health disparities, such as, for example, the training of minority investigators in research to address the needs of racial/ethnic minority populations. The ongoing support for training of investigators at various stages of their careers, through training grants, fellowships, career development awards, and other venues, will continue to be a critical component of NIH research efforts to improve public health.

Goals

Short-term Goals

- ▶ Identify areas in which the lack of technology or resources is limiting research progress, such as tools to measure energy balance in humans.
- ▶ Develop a comprehensive effort to promote the development of transdisciplinary teams of investigators, and to enhance training of investigators by incorporating training opportunities into large obesity-related initiatives in addition to continuing support for other research training programs.
- ▶ Identify research networks and translation and implementation networks addressing obesity prevention and treatment. Create a listing of networks and contacts to facilitate connections between research and implementation to facilitate the rapid translation of research evidence into practice.

Intermediate-term Goals

- ▶ Develop improved technologies, including e-technologies: 1) for monitoring dietary intake, physical activity, and psychosocial responses to environmental exposures related to obesity, 2) for use as potential intervention tools related to diet and physical activity, and 3) for use in e-health tools for consumers and patients that can effectively help them understand their health, identify appropriate behavior changes, and make informed decisions.
- ▶ In well-characterized clinical trial populations, test the utility of novel biomarkers to predict the progression of health conditions associated with obesity, or to predict the efficacy of therapeutic approaches for preventing or treating obesity or its associated health conditions.
- ▶ Develop comprehensive transdisciplinary networks of investigators that are well-connected to translation and implementation networks to ensure rapid translation of research evidence into policy, public health, and clinical efforts to prevent and treat obesity.

Research Topic

Translational Research

A clear goal of research is to progress from “bench to bedside,” that is, from findings obtained at the laboratory “bench” (for example, in a test tube or in a mouse model), to research in humans (clinical research), and ultimately to activities that improve health at a patient’s bedside or in the public-health arena. The reverse process, “bedside to bench

research,” is also valuable, as it brings knowledge gained in a clinical setting back to the laboratory for further exploration that may in turn spur new clinical endeavors. Research that helps speed these bidirectional knowledge transfers is important to ultimately improve the public health.

“Translational research” can refer either to moving results from basic research in the laboratory into clinical trials, or to bringing clinical trial results to public health. One type of effort that would be valuable to moving from basic to clinical research is the fostering of multidisciplinary research teams of basic and clinical researchers, as discussed previously. In going from clinical research to public health, translational research refers to testing the viability and feasibility of interventions delivered in “real-world” settings and examining their effectiveness in achieving change. Observational examination of activities actually delivered in practice can inform intervention research. Such research can bridge the link from controlled clinical studies to wider use in community or other real-world settings. For example, the NIH *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults* was published to guide practitioners in identifying and treating obesity. The guidelines were based on evidence from randomized controlled trials, many of which were conducted in specialized clinical settings at academic centers and used state-of-the-art behavioral approaches. The resultant guidelines recommend therapy for weight loss to include consumption of a decreased calorie, healthy, reduced-fat diet to help achieve caloric reduction, increased physical activity on a regular basis, and behavioral approaches to help achieve these behaviors. However, it is not clear what methods can promote the implementation of these interventions, or modifications of them, in a wide variety of real world settings and to a broad range of population subgroups. Community-based translational

research is one approach for addressing health disparities issues, for example, through translational research on culturally competent prevention, early intervention, and disease management strategies for diverse population groups.

Physicians are in an excellent position to counsel obese patients about lifestyle behaviors that contribute to obesity, provide treatment alternatives, oversee treatment, provide support, and monitor progress in scheduled office visits. However, delivering such care is not without challenges. Therefore, comprehensive healthcare systems that provide counseling for obesity and nutrition by other health providers (including dentists) may also be valuable. Research could contribute to development and testing of optimal approaches for the implementation of appropriate healthcare for obesity, including both lifestyle counseling and medical treatments when warranted. In addition to enhancing counseling approaches, it will be valuable to explore ways to trigger discussion of weight with patients by a physician or other healthcare provider. Studies evaluating the optimal role for registered dietitians, behavioral specialists, exercise specialists, nurses, and other non-physician healthcare professionals, and lay persons in obesity treatment will be beneficial. Effective approaches may require modifications of systems in which healthcare is delivered. The impact of reimbursement for obesity treatment on access to and delivery of care and on adherence to treatment should also be studied. In addition, community settings, such as schools, worksites, religious organizations, and neighborhoods, can be avenues through which interventions may be tested to determine their feasibility and effectiveness. Interventions devel-

oped, tested, and proven to be effective through methods of translational research are likely to be adopted by the healthcare system and to lead to substantial progress to combat the obesity problem and improve public health.

Goals

Short-term Goals

- ▶ Determine the practice patterns of physicians and other healthcare providers (including dentists) in providing counseling and other care for obesity, and examine factors associated with and barriers to treatment, including time limitations, training in obesity management, and reimbursement.
- ▶ Support efficacy and effectiveness research to define the role of social marketing and communication in efforts to control obesity at the individual and population level.
- ▶ Support research to identify effective approaches for combining strategies that involve health policy, media or marketing campaigns, and legislative action to influence public attitudes and practices in healthy eating and physical activity.

Intermediate to Long-term Goals

- ▶ Determine the impact of providing training in behavioral counseling skills and approaches to physicians, nutritionists, exercise physiologists, nurses, diabetes educators, dietitians, and other health professionals on the effectiveness of weight management treatment.
- ▶ Evaluate the potential for non-healthcare providers, such as teachers or peer counselors, to deliver weight management interventions.
- ▶ Evaluate the effectiveness of commercial and non-commercial (for example, self-help) settings for weight management interventions.
- ▶ Test intervention approaches for obesity prevention, weight control, and/or weight loss and its maintenance in real world settings, such as work sites, community organizations, and healthcare practices.

Research Topic

Disseminating the results of NIH research to the public and healthcare providers

It is critical to communicate the results of scientific research—including clinical trial results—to the public, healthcare providers, and the media. As with any disease or other medical condition, educational and informational efforts related to obesity should be tailored to different populations in culturally appropriate ways that provide effective communication. Additionally, encompassed within a focus on different ethnic dietary practices would be efforts to address the impact of potential changes in cultural practices experienced by offspring of those who immigrated to the U.S. and its environment of food abundance.

Behavioral and social scientists may contribute to developing culturally-appropriate health messages and campaigns, in collaboration with researchers from other disciplines and healthcare professionals.

The public further needs to be aware not only of the health risks associated with obesity, but also that prevention and treatment require the adoption of lifelong behaviors that are often difficult to embrace in today's environment. Different types of specific messages—such as those focusing on health, quality of life, or appearance—should be evaluated for their impacts on knowledge, attitudes, and behaviors. Additionally, messages that convey the health benefits of weight loss should also strive to avoid the potential for development of eating disorders and other psychosocial problems in susceptible persons, and to avoid increasing stigma faced by obese persons. Further, it is important to address the use of harmful weight loss strategies, such as smoking or inappropriately restrictive dietary intake.

One example of disseminating the results of research on obesity from the NIH to healthcare providers was the evidence-based review of pertinent research studies on obesity treatment and its compilation into the NIH *Clinical Guidelines on the Identification, Evaluation and Treatment of Overweight and Obesity in Adults*. This document involved the review of over 300 clinical trials by an expert panel and outlined the parameters for obesity treatment. These parameters included the development of appropriate measures for identification of at-risk patients, such as the BMI and waist circumference, as well as recommendations for appropriate treatment options for such patients.

As scientific research progresses, efforts will continue to enhance the development of science-based educational materials about weight control, obesity, and its associated health problems.

Goals

Short-term Goals

- ▶ Improve public awareness of the effects of overweight on disease risk and quality of life through public outreach efforts, especially those that target high-risk groups such as African Americans, Hispanic Americans, and American Indians.
- ▶ Partner with other governmental agencies (local, state, national) to support the evaluation of initiatives that translate successful healthy weight control strategies to policy, public health, and clinical practice, particularly within government-sponsored programs for prevention and treatment of obesity.
- ▶ Partner with private and public organizations involved in healthcare delivery to identify best practices and consider effective policies and approaches to facilitate translation of research relevant to weight control and dissemination into policy, public health, and clinical care and community settings.
- ▶ Collaborate across other public, non-profit, and private sectors to gain agreement and consistency on evidence-based intervention approaches that have the greatest promise of combating obesity at the population level.

- ▶ Include parents, peers, teachers, and community members in developing avenues for communication of research knowledge regarding prevention and treatment of obesity in children.

- ▶ Support social marketing research among different people, including those from diverse populations and their providers, to help strengthen the dissemination of evidence-based energy balance intervention approaches to the public, non-profit, and private sectors. Research should provide insight into specific life processes and how to effectively deliver the benefits of changes in diet and physical activity along with removing barriers.

Intermediate-term Goal

- ▶ Partner with and support the creation of integrated networks of public and private organizations working at local, state and national levels to translate and disseminate evidence-based successful, healthy weight control strategies into policy, public health and clinical practice.

Strategies and Opportunities for Achieving the Goals

This section includes efforts related to cross-cutting obesity research areas.

Ongoing Efforts

Descriptions of ongoing efforts are presented in Appendix B.

Plans under Development

Health Disparities—Addressing the Needs of Specific Populations

Research efforts addressing the needs of specific populations, such as children and racial/ethnic minorities, are found throughout the Strategic Plan document, as these efforts are integral and critical to research in the many scientific areas addressed, as well as to the education and outreach activities described in the Plan for disseminating the results of research to the public and healthcare providers.

Enhancing Research Resources and Fostering Multidisciplinary and Interdisciplinary Research Teams

Ancillary studies to obesity-related clinical trials:

The NIH has made substantial investments in a number of large-scale clinical trials and clinical research networks, to investigate obesity-related diseases and conditions in large numbers of participants. To maximize the value of the participation of the volunteers in these studies and the investment of the NIH, including, for example, analyses of biological samples obtained, the NIH is encouraging investigators to develop new ancillary studies for more in-depth investigation of mechanisms underlying diseases addressed by these

trials and networks. Such ancillary studies could include, for example, investigation of the genetic and environmental factors underlying obesity, of the pathogenesis of obesity and associated health conditions, of surrogate markers or biomarkers for obesity-related disease and therapeutic effects of interventions, and of new technologies for measurement of diet, physical activity and energy balance. This effort will also encourage scientists with expertise in basic research to work with clinical investigators. Examples of large-scale clinical trials that could accept ancillary studies through this effort include Look AHEAD (Action for Health in Diabetes) and the Diabetes Prevention Program Outcome Study, both of which are discussed elsewhere in the Strategic Plan; the Program to Reduce Incontinence by Diet and Exercise (PRIDE), which will evaluate the impact of weight loss on urinary incontinence in overweight and obese women; and several other trials and networks.

Partnerships between basic and clinical researchers in obesity: Several research efforts under development by the NIH will encourage collaborations between basic scientists and clinical researchers who work with obese individuals. These collaborations may occur within the context of ongoing major clinical trials and networks, or may be independent. The aim of these collaborations would be to gain a better understanding of obesity-related disease progression and of the mechanisms that mediate responses to therapies for obesity. Major progress in this area requires that true partnerships be encouraged through new mechanisms respecting contributions of both basic and clinical investigators and allowing for rapid translation of discoveries to the clinic for testing. Major planning efforts are now under way both within the NIH Obesity Research Task Force and as part of the broader NIH Roadmap Initiative (<http://nihroadmap.nih.gov/>) to develop mechanisms to meet this goal.

Trans-NIH intramural obesity initiative:

The Intramural Research Program (IRP) at the NIH provides a unique venue for facilitating obesity research. To address the epidemic of obesity in the U.S. and throughout the developed world, a coordinated approach is required that includes wide-ranging expertise and sophisticated infrastructure/technology that are available in the IRP but not at most institutions that conduct clinical research. Therefore, the NIH plans to create an “Obesity Clinical Research Center” (OCRC) in its IRP to generate new knowledge regarding the prevention, treatment, and underlying molecular mechanisms of obesity and its associated diseases. This planned Center will foster multidisciplinary approaches to obesity research in areas such as metabolism, endocrinology, nutrition, cardiovascular biology, gastroenterology, hepatology, genetics, and behavioral sciences. The Center will include a “magnet” approach, in which expertise and resources from across a wide-spectrum of the Intramural Research Program are focused on state-of-the-art clinical investigative strategies, laboratory support, and imaging capabilities to pursue obesity research in a synergistic manner.

Interdisciplinary Research Teams of the Future:

The increasing complexity of science requires a shift from the classical individual laboratory based investigation to a team approach requiring significant input and interaction among multiple investigators with different expertise. While this is a key piece of the NIH Roadmap, it is ideally exploited in the field of obesity. Not only do the contributors to obesity span the range of human activity, but the study of obesity requires the full breadth of scientific tools and approaches. Both methods and models are needed that can define the interactions between diverse input signals such as sensory cues (for example, smell, taste, sight), endocrine signals (such as insulin, leptin,

glucocorticoids, ghrelin), nutrient signals (glucose, cholesterol, free fatty acids) and neural signals transmitted through the brainstem. Not only will this require teams of investigators who understand brain, muscle, adipose, liver and gastrointestinal physiology, but it will also require the collaboration among investigators with expertise in the psychobiology of human behavior and those working at the developmental cusp of technologies to image tissue composition and function.

Education/Outreach and Translation Efforts

Educational materials for middle-school students:

The NIH is sponsoring the development of a curriculum for middle-school students on the science of energy balance, with lessons on caloric intake and physical activity.

Exploring the role of social marketing in the treatment and prevention of obesity:

The NIH will explore the potential for a targeted effort at social marketing to promote beneficial changes in energy balance. The initiative may include efforts to identify—via extant evidence syntheses—the evidence-based energy balance interventions that are ready for dissemination to the public, non-profit and private sector; conduct an “environmental scan” to identify the messages, marketing offers and policies that are currently affecting energy balance in the population; coordinate across the NIH and with other HHS efforts, and cultivate appropriate partnerships in the non-profit and private sectors; conduct analysis of existing data to identify potential target audiences and key intermediaries; and conduct social marketing research.

Concepts for future research

Enabling Technologies

Bioengineering approaches for prevention and treatment of overweight and obesity: A potential initiative is under consideration in this area. The purpose of this initiative would be to bring state-of-the-art bioengineering technology to address the range of practical problems in energy balance, intake, and expenditure that are associated with the epidemic of obesity in American adults and children. Sensors, devices, imaging, and other approaches would be developed and evaluated through collaborations between biomedical engineers and scientists with expertise in obesity. The goal is to provide technologies and tools to facilitate research and support behavioral change.

A SNAPSHOT IN TIME OF A DYNAMIC PLANNING PROCESS

The multi-faceted and ambitious obesity research plans described in this document necessarily represent a snapshot in time of an ongoing strategic planning process at NIH. To achieve the goals set forth in the Plan, the NIH will continue its planning of future research efforts based on new knowledge, opportunities, and challenges that arise from current scientific endeavors. A set pathway toward achieving the goals thus cannot remain rigidly fixed; rather, the planning of new research efforts must be dynamic. As research accelerates and new discoveries come to light, the NIH will continually refine, reassess, and build upon its obesity research planning efforts so as to deploy future investments toward the most promising scientific opportunities and critical public health issues.

As a way to keep the research community informed of this dynamic planning process, and as a venue for facilitating future progress in obesity research, the NIH Obesity Research Task Force has developed an obesity research Web site to enhance the communication of information about new NIH-sponsored funding opportunities as they are launched, and to announce NIH-sponsored scientific meetings (<http://obesityresearch.nih.gov/>). The Web site is intended to assist and encourage researchers in their pursuit of further understanding of obesity and its link to many diseases and other health conditions, and in their investigations of potential new prevention and treatment strategies.

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APPENDIX A

Examples of NIH-Supported Obesity Research Advances

Many ongoing studies and scientific opportunities for future research build upon past research investments and accomplishments. Although a comprehensive review of past research findings is beyond the scope of this future-oriented planning document, examples of NIH-supported research advances are highlighted

below to illustrate the types of scientific discoveries that are propelling the obesity research strategic planning process. The examples below include research advances emanating from NIH-initiated efforts and those resulting from investigator-initiated efforts.

Fundamental and Clinical Research Directed at Obesity Prevention and Treatment

NIH-funded researchers are elucidating the roles of a vast array of biological molecules in processes that control energy balance. These include, for example, hormones produced by the brain, gut, and fat cells, which regulate appetite, the storage of excess calories as fat, and energy expenditure. These molecules traverse an elaborate network of signaling pathways connecting many organs of the body, including a region of the brain called the hypothalamus, to achieve an integrated control of metabolism. By providing new “targets”—molecules or biological signaling pathways—for drug development, this research is contributing to the design of potential new treatment strategies by academic researchers, as well as the pharmaceutical industry. Drugs that

home in on one of these targets could beneficially affect appetite, food absorption, or energy expenditure. Genetic studies in animals and humans are beginning to provide yet another avenue for the discovery of novel molecules or biological pathways linked to obesity. For example, researchers have found that mutations in a particular gene, known from studies in mice to be involved in regulating food intake and energy balance, are associated with some rare cases of childhood obesity; other genetic variations associated with obesity in humans are also being revealed. Genetic studies may well form the basis for selection of a particular treatment or preventive strategy tailored to an individual patient or subpopulation for optimal benefit.

Examples of NIH-supported Research Advances: Biological Molecules and Signaling Pathways that Regulate Energy Balance

- ▶ In 1994, scientists made the ground-breaking discovery of the hormone leptin. The fact that leptin is secreted by fat cells drastically altered the former view of fat tissue as a passive storehouse for energy. Fat cells actively communicate with the brain and other organs, through hormones such as leptin, to regulate appetite and metabolism. Leptin was identified first in obese mice and then in people; administration of leptin was hoped to be a cure for obesity. A few people in the world completely lack leptin, resulting in severe obesity from infancy, and leptin administration in these rare individuals causes substantial weight loss. However, common forms of obesity are likely associated with a resistance to leptin's actions because most obese people have very high levels of leptin. Scientists are currently delving into the molecular mechanisms by which leptin transmits its signals; this research is casting light on how obesity may develop and might be treated.
- ▶ Research into the molecular regulation of energy balance has also uncovered new pathways and molecules that influence energy intake, storage, and expenditure. Notably, one such hormone, ghrelin, stimulates appetite just before meals. Ghrelin is primarily secreted by the stomach, but is also produced in the brain. Increased levels of this appetite-inducing hormone were found in obese individuals following diet-induced weight loss. This finding provides a potential explanation for the difficulty people experience in maintaining weight loss. Ghrelin thus is an attractive target for drug development.

- ▶ PYY₃₋₃₆, a hormone also produced in the gut, is secreted after the initiation of a meal and may serve as a satiety factor (meal-termination signal). Infusions of this hormone were shown to reduce appetite and decrease caloric intake, even when the volunteers in the study were presented with a free-choice buffet meal. This hormone is also being considered as a potential prototype for drug development.

Clinical research into obesity prevention and treatment, which includes changes in diet and physical activity, is illuminating both the power of lifestyle interventions and the extraordinary challenges of implementing behavioral approaches. Continued behavioral research should greatly enhance the understanding of factors that contribute to obesity and may assist with future design of both pharmacologic and lifestyle interventions. Nutritional research and studies assessing the effects of different types and amounts of physical activity are also helping to inform lifestyle-based interventions.

Examples of NIH-supported Research Advances: Clinical Studies in Obesity Prevention and Treatment Through Lifestyle Interventions

- ▶ The Diabetes Prevention Program (DPP) clinical trial tested both medical and lifestyle interventions as means for the possible prevention or delay of type 2 diabetes in those at risk for this disease. The trial included over 3,000 participants, of whom nearly one-half were from minority groups; the study also recruited significant numbers of women as participants. The participants were randomly assigned to one of three groups: lifestyle intervention, medical intervention with the diabetes drug

metformin, or a control group. Of particular relevance to overweight and obesity, the lifestyle intervention demonstrated a 58 percent reduced risk of developing type 2 diabetes—a disease for which obesity is a strong risk factor—in a high-risk population: the participants had elevated blood glucose levels and were overweight. The metformin intervention reduced diabetes risk by 31 percent. Importantly, the lifestyle modification worked well in both men and women, and in all ethnic groups studied. The success of this arm of the DPP trial was predicated on extensive previous research on behavior modification. Importantly, the dramatic health benefit seen in the DPP did not require extreme weight loss, but rather only modest weight loss and exercise. This concept is now part of a new educational campaign to translate the DPP results, called “Small Steps. Big Rewards. Prevent Type 2 Diabetes.”

- ▶ An active area of research is the evaluation of different types of diets for their effectiveness in weight loss. For example, in one interesting series of studies, scientists are exploring dietary manipulation to decrease caloric consumption and increase satiety. Over the short-term, decreases in the energy density of foods (calories per gram of food) were found to lead to decreased food intake, independent of fat content. While long-term studies are needed, these results suggest a possible strategy for reducing food intake.
- ▶ Investigators have confirmed hypotheses that food portion sizes, both in fast-food establishments and in the home, increased markedly from the late 1970s to the late 1990s. Relevant to this finding, researchers have also shown, in a separate study, that larger portion sizes lead to greater food consumption.
- ▶ Complementing studies on diet, investigators are also continuing research on physical activity and sedentary behaviors. For example, a recent trial demonstrated beneficial effects on weight of moderate-intensity exercise in young overweight or moderately obese men and women. In another study, researchers reported that sedentary behaviors—especially television watching—are predictive of significantly increased risk of obesity and type 2 diabetes in women. One study showed that an intervention that reduced television watching and video game use had a favorable impact on decreasing weight gain in children.
- ▶ Research to identify successful weight-loss strategies has been enhanced through support of the National Weight Control Registry, a study of individuals who have managed to lose weight successfully over the long term.
- ▶ The Trial of Nonpharmacologic Interventions in the Elderly (TONE) study tested the effects on blood pressure control of three types of lifestyle interventions (weight loss alone, sodium reduction alone, and weight loss in combination with sodium reduction) compared to usual care in 875 older hypertensive men and women. All versions of the lifestyle intervention (sodium reduction, weight loss, and combination of the two) reduced events indicating poor blood pressure control, including the need to resume use of blood pressure medication.

- ▶ The PATHWAYS study tested the effectiveness of a culturally appropriate multicomponent school-based intervention to prevent obesity in American Indian elementary school students in a randomized school trial. The intervention was conducted at 21 schools, and 20 additional schools were studied for comparison purposes. The intervention focused on promotion of healthful eating and physical activity behaviors and environments. In contrast to the comparison group, the intervention resulted in significantly greater knowledge of the eating and physical activity health concepts and skills that were taught, a reduction in saturated and total fat served in school lunches, a reduction in reported intake of saturated and total fat during a typical 24-hour period, and a higher level of reported physical activity. However, the study found no significant differences in physical activity between children in the intervention schools and those in the comparison schools, with physical activity measured by a motion sensor, or in percent body fat.
- ▶ Brain dopamine is a neurotransmitter important in modulating the rewarding properties of food, drugs, and other stimuli. A preliminary clinical neurobiological study has been done using brain imaging technology to examine brain dopamine activity in a small number of obese individuals. In this study, brain dopamine activity was found to be abnormal: the obese individuals had significantly reduced amounts of brain dopamine D₂ receptors in specific regions of the brain, and these reductions were in proportion to BMI. These low levels of dopamine D₂ receptors have been observed in individuals addicted to various types of drugs and suggest that reductions in D₂ receptors might be associated with addictive behavior. Dopamine deficiency in some obese individuals might contribute to and perpetuate pathological eating as a way to compensate for decreased dopamine activation in these areas. Therefore, strategies that ultimately improve dopamine function could lead to new therapeutic approaches for obesity treatment in some individuals.

Another vital aspect of NIH efforts is epidemiologic research to understand the patterns of obesity in society. These types of studies may be useful as a way to assess where interventions may be especially valuable.

Examples of NIH-supported Research Advances: Epidemiologic Research

- ▶ The Coronary Artery Risk Development in Young Adults (CARDIA) long-term study has been examining the distribution and evolution of coronary heart disease risk factors in 5,115 African American and white men and women, aged 18-30 years at entry, from a wide range of educational levels. The original goal of the study was to identify the determinants of major cardiovascular disease risk factors, particularly obesity, hypertension, and hyperlipidemia, during the critical years of transition of young adulthood. There have been striking increases in obesity among CARDIA participants over 15 years—from 6 percent to 25 percent in white men, 8 percent to 24 percent in white women, 11 percent to 37 percent in African American men, and 21 percent to 51 percent in African American women. Body Mass Index (BMI) increases were greatest at the upper ranges of BMI, with large weight gains more common among those already overweight at baseline. Most of the weight increase was due to cohort effects (i.e., the experience of people who reach the same age at the same time) rather than aging trends; 30-year-olds in CARDIA in 1995 were much heavier than 30-year-olds at entry to the study in 1985. These trends do not appear to be abating, with weight gain being greatest among African American women and least among white women. The largest increases due to aging were observed when participants were in their early to mid-20s. Additional research related to CARDIA is ongoing.

- ▶ The Framingham Heart Study is a longitudinal investigation of constitutional, environmental, and genetic factors influencing the development of cardiovascular disease in over 14,000 men and women in three generations. Multiple measures of weight, height, girth and selected measures of skinfold thickness have been performed. In recent years there has been significant research on the role of BMI on the incidence of coronary heart disease (CHD), stroke and congestive heart failure (CHF), and cancer. In Framingham, overweight status was related to incident hypertension but less so to hypercholesterolemia. Other results indicate that sustained weight loss notably reduces the risk of diabetes. The Framingham Heart Study is continuing to provide valuable information.
- ▶ The Strong Heart Study and Strong Heart Family Study were initiated to estimate levels of cardiovascular disease risk factors in 4,500 American Indian men and women aged 45 to 74 and their families from three geographically diverse centers. The prevalence of overweight and obesity in these communities is among the highest in the world. More than 80 percent of women are overweight or obese based on the cut-points included in NIH clinical guidelines. Obesity in this cohort is a risk factor for diabetes, hypertension, low HDL-cholesterol, and high triglycerides. It is also related to many cardiac structure and function measures including left ventricular mass, relative wall thickness, cardiac output and total peripheral resistance. Cardiac output and stroke volume have been more strongly related to fat free mass than adipose mass. Further studies are currently ongoing.

Research on the Link Between Obesity and Serious Health Problems

As noted, obesity is associated with numerous diseases and disorders. These include type 2 diabetes, cardiovascular disease, some types of cancer, depression, and many other medical conditions. Yet, not all overweight and obese people develop these health conditions. Thus, research is intensifying to identify aspects of obesity, or markers, associated with disease risk. This research may lead to the development of new prevention, diagnostic, and treatment paradigms.

Examples of NIH-supported Research Advances: The Link Between Obesity and Health Problems

- ▶ Obesity leads to type 2 diabetes in adolescents. The incidence of type 2 diabetes in adolescents has increased by a factor of ten over the past 15 years as a consequence of the epidemic of obesity in childhood and adolescence. A state of insulin resistance and impaired glucose tolerance precedes the onset of clinical diabetes. NIH-supported research has shown that 20 to 25 percent of obese children and adolescents have impaired glucose tolerance on oral glucose tolerance testing, and that 4 percent of obese adolescents have clinical diabetes with elevated levels of fasting plasma glucose. These findings underscore the need for primary care practitioners to perform oral glucose tolerance testing on obese children in their practices.

- ▶ NIH-supported investigators have shown that obesity in adulthood is an established risk factor for hypertension, type 2 diabetes, cardiovascular disease, and some kinds of cancer. They have also shown that overweight in childhood tracks with fidelity into adulthood. Recent research has shown that the earlier overweight develops in childhood (the adiposity rebound), the more severe the overweight/obesity will be in early adulthood with the attendant early appearance of health problems.
- ▶ Beginning in 1990, the CHIC Study (Cardiovascular Health in Children and Youth Study) has collected data on almost 4,000 school children and adolescents in North Carolina—from ages 8 through 16. The risk factors being monitored are serum cholesterol, blood pressure, obesity, cardiovascular fitness, and certain behaviors, such as tobacco use, eating habits and physical activity. The 45 schools in the study are located in 15 counties across the State, including both rural and urban areas. The first of three CHIC studies indicated that the cholesterol level dropped more in the group receiving a classroom-based intervention than in small groups. Body fat dropped in both groups, aerobic power increased in both groups, and diastolic blood pressure did not rise as much in both groups as in the control group. CHIC II, the second study, showed that a combination of physical education and health education had a greater favorable impact on cholesterol, blood pressure, body fat and aerobic fitness than either approach alone. The current continuation of the Cardiovascular Health in Children and Youth Study (CHIC III) will investigate the childhood development of the multiple metabolic syndrome (MMS). This syndrome consists of a clustering of related metabolic abnormalities including high blood insulin levels, blood glucose abnormalities, abnormal blood fat levels (high triglyceride and low

levels of the good high-density lipoprotein cholesterol), high blood pressure, and obesity. This study focuses on the problem of obesity and other precursors to type 2 diabetes and cardiovascular disease.

- ▶ It is not only the total amount of fat that is relevant to health, but also its location. Visceral fat (fat surrounding the internal organs in the abdomen), rather than total body fat, is the better predictor of obesity-associated conditions such as type 2 diabetes. Scientists have generated a mouse model of visceral obesity by genetically engineering fat tissue of the mice to produce extra amounts of the enzyme 11 beta HSD-1. This enzyme was known to be involved in producing active glucocorticoids from inactive forms, and glucocorticoids have been shown to influence the distribution of body fat and to regulate fat cell functioning. Further, elevated levels of the 11 beta HSD-1 enzyme are indeed seen in human obesity. Also, a rare human disease, Cushing's syndrome, is characterized by excess circulating glucocorticoids, and patients with this syndrome develop visceral obesity. Mice that were engineered to overproduce 11 beta HSD-1 specifically in fat cells not only had visceral obesity, but also developed hypertension, abnormal blood lipids, and insulin-resistance, a cluster of symptoms found in the metabolic syndrome. The study of this mouse model has implications for developing new treatment strategies for obesity and the metabolic syndrome.
- ▶ Inappropriate accumulation of fat in tissues such as muscle and liver has deleterious effects on metabolic function. In studies in mice that shed light on the body's regulation of fat levels, the hormone leptin was shown to reduce synthesis of fatty acids in liver and to stimulate fatty-acid oxidation (fat "burning") in skeletal muscle.

- ▶ The majority of patients with type 2 diabetes are overweight or obese, and scientists are beginning to find the biological molecules that connect obesity to a condition called insulin resistance, a precursor to type 2 diabetes. (The hormone insulin regulates blood sugar levels and influences a variety of other cellular processes.) As one example of this area of study, researchers found that insulin resistance in a mouse model may result in part from too little of a signaling protein called adiponectin. Adiponectin is secreted by fat cells and appears to be positively correlated with insulin sensitivity. Scientists have also observed decreased adiponectin levels associated with obesity and type 2 diabetes in humans. Recently, in another study in mice, scientists found evidence that adiponectin may decrease body weight by acting in the brain to stimulate energy expenditure. In addition to adiponectin, other signaling proteins are also involved in the link between obesity and insulin resistance.
- ▶ Research over a number of years with the Pima Indians of Arizona, a group with extremely high rates of overweight, obesity and type 2 diabetes, has shed light on the contributions of genetics and environment to these conditions and on other aspects of obesity. These studies have also found that the baby of a mother who has diabetes during pregnancy has a very high risk of becoming overweight and developing diabetes as a young adult. Thus, in addition to inherited genetic factors, the environment of the womb can contribute to overweight and diabetes. These results underscore that efforts to prevent type 2 diabetes at early ages may not only improve the health of young women, but may also benefit their offspring.
- ▶ NIH-supported investigators have shown that obesity in adulthood is an established risk factor for cancers of the colon, renal cell, thyroid, endometrium, and postmenopausal breast, and adenocarcinoma of the esophagus and gastric cardia. Extensive data provide convincing evidence of a positive association between overweight and obesity and adverse changes in breast cancer prognosis and mortality. Research has demonstrated that two major mechanisms underlying these associations include exposure to sex steroids, and insulin and insulin-like growth factors. Research also documents that physical inactivity is an established risk factor for cancers of the colon and breast. Physical activity is associated with a 50 percent reduction in colon cancer and a 30 to 40 percent reduction in breast cancer. Some evidence suggests that the protective effect of physical activity for breast cancer may be limited to women who are not overweight or obese, consistent with one hypothesis that physical activity may reduce risk through prevention of obesity.
- ▶ A significant minority of obese individuals seeking treatment for obesity meet criteria for binge eating disorder, in which individuals eat large amounts of food while experiencing a sense of loss of control. Binge eating disorder has been associated with increased weight gain and more severe obesity. Although treatment of eating disorders in the absence of obesity treatment does not result in weight loss, several NIH-supported studies found that amelioration of binge eating does result in small weight losses and decreased weight gain over time. Better understanding of factors underlying binge eating in children and adults may lead to effective strategies for prevention of both eating disorders and obesity in at-risk populations.

Examples of NIH Efforts to Bring the Results of NIH-Supported Research to the Public and Healthcare Professionals

The NIH supports the development of educational and informational materials for the public and for healthcare providers to help convey important health information. In addition to making these materials available on the Internet and in printed form, the NIH also develops and supports programs to actively

disseminate health information. Examples include activities of the NIDDK's Weight-control Information Network (WIN) and the NHLBI's Obesity Education Initiative. These and other efforts are ongoing; additional information is provided elsewhere in the document.

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APPENDIX B

Ongoing NIH Efforts

Introduction

This Appendix highlights examples of ongoing NIH efforts relevant to obesity research. These efforts are among the strategies and opportunities supported by the NIH to achieve its goals for:

- ▶ research toward preventing and treating obesity through lifestyle modification;
- ▶ research toward preventing and treating obesity through pharmacologic, surgical, or other medical approaches;
- ▶ research toward breaking the link between obesity and its associated health conditions; and
- ▶ cross-cutting research topics, including technologies, fostering of multidisciplinary and interdisciplinary research teams, investigator training, translational research and education/outreach efforts.

Organization of the Ongoing NIH Efforts Appendix

Numerous NIH-supported efforts relevant to obesity research are ongoing. In parallel to the descriptions of future efforts, presented earlier in the Strategic Plan document, the descriptions of the ongoing efforts in this Appendix are organized under the scientific themes listed previously. One exception to this organization is a description of the program of Clinical Nutrition Research Units (CNRUs) and Obesity/Nutrition Research Centers (ONRCs). Because of the multifaceted nature of these Centers, the description of this program is given at the beginning of this Appendix. Following this, the individual scientific themes and associated ongoing efforts are presented.

Focus of the Descriptions on Efforts Initiated by the NIH Through Research Solicitations

As noted, the NIH supports investigator-initiated research projects and initiates research efforts through solicitations for grant applications. Investigator-initiated research represents a substantial portion of the NIH funding portfolio, and the NIH will continue vigorous support of these efforts. The Strategic Plan is focused on NIH-initiated efforts, developed in consultation with the external scientific and lay community. These efforts complement the research projects initiated by investigators in several ways, for example, by encouraging further studies in areas of particular scientific opportunity or interest and in fields in which there are gaps in knowledge or particular barriers to be overcome.

Examples of Ongoing NIH Efforts

Clinical Nutrition Research Units (CNRUs) and Obesity/Nutrition Research Centers (ONRCs):

The CNRU/ONRC program provides important resources for the obesity research community. There are ten CNRUs and four ONRCs, located throughout the country. These Centers are integrated arrays of research, shared resources, educational, clinical, and training opportunities. These Centers pursue basic and clinical research, including such cross-cutting areas as multidisciplinary research and translational research, and offer a rich environment for research training related to obesity and nutritional sciences.

Advances in obesity research are derived from such fundamental disciplines as biochemistry, molecular biology, genetics, and physiology; and such medical specialties as internal medicine, pediatrics, and surgery. Because of its interdisciplinary nature, obesity research can benefit from close interactions among researchers, health services providers, and educators. Supported by the NIH, the core centers for shared research facilities at CNRUs and ONRCs are a valuable way to promote multidisciplinary interactions, fostering and strengthening obesity research within a broad nutritional science context.

The CNRUs and ONRCs conduct research on treatment and prevention of obesity and eating disorders, understanding of the control and modulation of energy metabolism as related to obesity, and understanding and treatment of other health conditions associated with abnormalities of energy balance and weight management. As one objective, these Centers strive to promote basic and clinical science studies to advance understanding of the complex interrelationships among genetic factors and the environment in obesity and other health conditions, such as diabetes, cardiovascular disease, and cancer. The CNRUs/ONRCs are poised to stimulate and support development and use of state-of-the-art techniques

to study nutritional factors and their influence on these and other health conditions. Another objective of the Centers is to encourage translational studies that apply newer basic science findings to the diagnosis and management of obesity and other chronic health conditions.

All CNRUs and ONRCs are required to conduct clinical studies. The clinical investigation component facilitates translation of research into practical treatment strategies for patients, provides Center investigators with clinical samples and patient data needed for their research, and serves as a bridge between clinical and basic science investigators. Most of the Centers have a clinic population with adequate representation of women and minorities who can readily participate in research studies. The availability of such a population plays a major role in attracting investigators to the field of obesity research, and also can facilitate the design of pilot and feasibility projects (discussed below). The emphasis on clinical research in the CNRUs and ONRCs further provides a natural interaction with the NIH-supported General Clinical Research Centers (GCRCs). The GCRCs are an additional resource for experimental design and instrumentation to advance the pursuit of pathophysiological mechanisms of obesity-related diseases in humans.

Another valuable aspect of the CNRUs and ONRCs is an associated pilot and feasibility program. This program provides support for new investigators or for established investigators who are moving into areas of research relevant to the goals of the Centers. Projects evaluating the effectiveness of model programs for translating research in biomedical and behavioral science into routine clinical care also are encouraged. The combination of the shared core resources, clinical research expertise, and support for pilot and feasibility studies also permits the CNRUs

and ONRCs a way to move quickly to study “natural experiments.” For example, protocols could be designed to assess the efficacy of proposed policy changes in schools concerning food offerings and/or physical activity, or to study obesity-focused efforts of food companies or restaurants.

Finally, many of the CNRUs/ONRCs are co-located at institutions with Schools of Public Health and CDC-supported Prevention Centers. Thus, these locations should be primed to respond to new initiatives, especially those targeting prevention at the community and population level.

Preventing and Treating Obesity Through Behavioral and Environmental Approaches To Modify Lifestyle

Environmental approaches to obesity prevention:

As a result of a recently launched NIH initiative in this area, a variety of new studies are now under way to develop and test environmental modifications aimed toward preventing obesity in children as well as adults. Environments targeted by these studies that are relevant to children include, for example, child care centers, schools, after-school programs, and the home; studies relevant to adults include, for example, a cafeteria-based study based in a community center. In addition to designing interventions to be tested, two of the projects will be “natural experiments” to evaluate the impact on health outcomes of new school policies, developed by policy-makers in Seattle and California, that relate to commercial advertising, the sale of energy-dense foods, and other issues. Among the studies being supported as a result of this initiative, some have a particular focus on minority populations disproportionately affected by obesity, including African Americans and American Indians.

Diabetes Prevention Program Outcome Study

(DPPOS): A follow-up study of participants in the DPP clinical trial (described previously) will examine the durability of the DPP interventions on prevention or delay of type 2 diabetes and its cardiovascular complications; heart disease is the major cause of death in people with type 2 diabetes. The DPPOS will additionally examine the ability to maintain weight loss in the participants over extended periods of time.

Look AHEAD (Action for Health in Diabetes)

clinical trial: This multi-center, NIH-sponsored clinical trial will examine the health effects of an intervention designed to achieve and maintain weight loss over the long term through decreased caloric intake and increased physical activity. Look AHEAD has a goal of enrolling 5,000 obese patients with type 2 diabetes, including both men and women and members of minority groups, and following them for up to 11.5 years to study the impact of the weight loss intervention on cardiovascular disease, the complication of diabetes that causes the greatest rates of illness and death.

National Health and Nutrition Examination Survey

(NHANES): The NIH provides additional resources to NHANES, a series of surveys conducted by the National Center for Health Statistics of the CDC. The goals of NHANES include estimating the number of people in the U.S. who have selected diseases, analyzing risk factors for diseases, and studying the relationship between diet, nutrition, physical activity, and health. Measurement of body composition and cardiorespiratory fitness are two of the components of NHANES currently supported by the NIH. The body composition measure will provide information on fat mass and percent body fat for the U.S. population, and the cardiorespiratory fitness measure will provide information on fitness for those ages 12 to 49 years. These data provide detail beyond body mass index and reported physical activity to be linked with other

important health status and public health information. In addition, the NIH has supported improvements in the methods for assessing diet and physical activity, including the addition of an objective measure of physical activity—key elements for understanding population targets for interventions to prevent and treat obesity. The NIH will also explore the potential of supporting a longitudinal component to NHANES to examine changes in weight over the lifetime in diverse population groups.

National and regional surveillance of health behaviors: The NIH provides support for cancer control supplements and other data elements within the National Health Interview Survey and the California Health Interview Survey. These surveys result in representative data concerning diverse health behaviors, including diet and physical activity. Current NIH efforts are focusing on using these surveys to better understand disparities in levels of physical activity among different race/ethnic groups and to develop capacity for analyzing associations between the environment and physical activity. Such efforts complement data from NHANES because they provide larger samples for specific racial and ethnic groups at high risk for obesity and more extensive coverage of regional and state diversity in obesity related health behaviors.

Weight-loss maintenance: Because maintenance of weight loss is a critical yet particularly difficult element of obesity treatment and prevention, the newly-launched Weight Loss Maintenance Trial will compare different strategies for maintaining weight loss over a period of 2½ years in approximately 800 adults who are at high risk for cardiovascular disease and who are successful in losing a targeted amount of weight over the short term through lifestyle changes.

Long-term evaluation of factors associated with childhood obesity or its associated health problems:

Investigators in the intramural program at NIH are conducting a longitudinal study in which 250 children who are either overweight or at risk for overweight are extensively evaluated for factors that may predict development of obesity or its associated health conditions, including genetic variation, metabolic and cardiovascular differences, food intake, total and resting energy expenditure, psychological functioning, eating disorders, and physical activity behaviors. These children are being followed for 15 years, and should provide valuable information on risks for the development of obesity and its medical complications.

The Girls Health Enrichment Multi-site Studies (GEMS):

This research effort is a two-phase program to develop and pilot-test interventions to prevent obesity in African American girls ages 8 to 10 years, a group at high risk of developing obesity. During Phase 1, several distinct interventions addressing diet, physical activity, and psychosocial and family influences were developed and pilot tested. During Phase 2, two field centers are testing separate 2-year interventions to reduce excessive weight gain in African American girls ages 8-10 years. One study is testing a family-based program that counsels and teaches 300 girls and their parents or caregivers to eat healthy diets, drink fewer sweetened beverages, and increase their physical activity. The second study of 260 girls is testing an intervention that encourages girls to attend after-school dance classes set up in the community to increase their physical activity and also delivers a home-based intervention to reduce girls' TV watching to reduce the amount of time they are sedentary and exposed to food advertising and eating opportunities.

The PREMIER trial—to determine the effectiveness of multicomponent lifestyle intervention programs in lowering blood pressure: A total of 810 participants were randomly assigned to receive one of 3 interventions over an 18 month period: 1) an intensive behavioral intervention to facilitate their achieving lifestyle changes that are currently recommended for blood pressure control—reduced salt intake, increased physical activity, and weight control or weight loss, as needed; 2) this same intervention coupled with a behavioral intervention to promote consumption of the DASH diet (an eating pattern rich in fruits, vegetables, and low fat dairy products; low in total and saturated fat and cholesterol; and moderately high in protein), which has been shown to lower blood pressure; or 3) advice alone.

The Dietary Composition, Obesity, and Cardiovascular Risk study: This study investigates the effects of energy density and three different macronutrient (protein, fat, carbohydrate) compositions of diet on coronary heart disease risk factors (LDL-cholesterol, HDL-cholesterol, remnant lipoprotein c, Lp(a) cholesterol, insulin, glycosylated hemoglobin, glucose, and blood pressure) in the fasting and nonfasting state (4 hours after a meal) in 80 men and women (men ages 50 to 67 years and postmenopausal women under 65 years) with elevated LDL-cholesterol (130 mg/dL or greater) and overweight or obese (BMI 28-38 kg/m²). A 12-week controlled diet feeding study followed by participants' preparing their own foods on their assigned diets for 1 year investigates the effects of energy density and various macronutrient composition (calories, fat, protein, carbohydrate, and dietary glycemic index) on energy balance and cardiovascular disease risk factors such as body weight and composition, physical activity, blood pressure, and plasma lipoproteins. This study plans to find out whether diets low in caloric density, regardless of overall fat intake or glycemic index, will have a more favorable effect on coronary heart disease risk factors, body weight and composition, and energy expenditure than a diet with higher caloric density and high glycemic index.

Dietary Macronutrients and Weight Loss: This trial investigates whether the macronutrient composition of the diet (the relative amount of fat, protein, and carbohydrate) can help promote weight loss and its maintenance. The trial compares the effects on weight loss and weight maintenance of four diets differing in macronutrient composition in 800 overweight or obese adults over a two-year period. The diets are all low in saturated fat. The four diets are a moderate fat diet and a low fat diet, each at two levels of protein. Participants are counseled to follow these diets using a state-of-the art behavioral program.

Low and high carbohydrate diets: The Safety and Efficacy of Low and High Carbohydrate Diets study is assessing the short-term and long-term clinical effects of different diets in 360 obese men and women. Participants in a 26-week behavioral weight loss program will be randomized to a diet featuring low carbohydrate, unlimited fat and protein, or to a conventional diet of high carbohydrate and low fat. Short-term (weeks 12-26) and long-term (weeks 52-104) effects of each dietary approach will be evaluated and compared in terms of changes in weight and body composition, metabolic and organ function, and exercise endurance.

Behavioral Change Consortium: This initiative was designed to stimulate investigations of innovative strategies designed to achieve long-term healthy behavior change. A large number of the funded projects are focusing specifically on physical activity and/or dietary behaviors. These projects include The SENIOR Project; Youth Environments Promoting Nutrition and Activity; Promoting Healthy Lifestyles: Alternative Models' Effects; Project HOPE; Exercise Advice by Human or Computer; Reducing Disease Risk in Low-income, Postpartum Women; and Health Promotion Through Black Churches. In addition, consortia working groups in nutrition and physical activity have been established to coordinate cross-site analyses of common research measures.

Maintenance of long-term behavior change: As a result of another NIH effort, new research is beginning on the biopsychosocial processes and interventions that target long-term maintenance of behavior change, including behavior relevant to overweight and obesity such as physical activity.

Obesity and the built environment—Improving public health through community design: The built environment encompasses all of the buildings, spaces, and products created or modified by people, including, for example: buildings (housing, schools, workplaces), land use (industrial or residential), public resources (parks, museums), zoning regulations, and transportation systems. An NIH-sponsored conference was held to provide a forum to discuss how different elements of the built environment may contribute to obesity via access to food and physical activity, and how environmental health research and interventions could address this public health problem. The goals of the conference included developing research and practice agendas to examine the relationship between the built environment and obesity, enhancing inter-agency coordination and partnerships, and examining evidence-based strategies for intervention. Results of this conference are now being considered in the planning of future research efforts.

Preventing and Treating Obesity Through Pharmacologic, Surgical, or Other Medical Approaches

Life-cycle of a fat cell: A new series of NIH-supported studies is characterizing how fat cells are formed and what determines their numbers and location in the body. Knowledge gained from this research will help in the understanding of obesity and other metabolic conditions.

Calcium as a potential supplement to prevent weight gain: Intramural NIH investigators are studying the role of calcium supplementation for prevention of weight gain. An ongoing 340-person randomized, controlled clinical trial of dietary supplementation with 1500 mg/d of calcium carbonate will determine whether calcium intake, which is considered an easily modifiable dietary factor, can affect future weight gain in overweight and obese adults.

Investigations of drug therapy in children and adolescents: Therapy for significantly overweight children and adolescents with obesity-related health conditions is also being studied by intramural investigators. Two ongoing randomized, placebo-controlled trials in the NIH Intramural Research Program are studying promising pharmacologic interventions: metformin for children ages 6 to 12 years, and orlistat for adolescents, ages 12 to 17 years.

Bariatric surgery: For people who are extremely obese, expected weight loss from behavior change alone may not be sufficient to have a major impact on health and is unlikely to be sustained. Bariatric surgical procedures, which restrict stomach size and/or lead to decreased absorption of nutrients, are being increasingly performed to treat severe obesity. These procedures can have dramatic benefits (such as improved glycemic control or even reversal of type 2 diabetes), but also carry substantial risks, including death. The NIH has now established a Bariatric Surgery Clinical Research Consortium, the Longitudinal Assessment of Bariatric Surgery (LABS), to facilitate and accelerate research in this area. This consortium will help pool the necessary clinical expertise and administrative resources to facilitate the conduct of multiple and novel clinical studies in a timely, efficient manner. Development of a database using standardized definitions, clinical protocols, and data collection instruments will enhance the ability to provide meaningful evidence-based recommendations for patient evaluation, selection, and follow-up care. This database, in turn, will promote rapid dissemination of research findings to healthcare professionals. In addition, this consortium will serve as a resource for basic and clinical studies which can explore the mechanisms by which surgery affects obesity-related comorbid conditions, energy expenditure, nutrient partitioning, appetitive behaviors, and psychosocial factors. This may lead to improved understanding of the factors underlying the development of obesity, with implications for new strategies for prevention and treatment.

Beyond BMI—Identifying additional traits associated with obesity that could facilitate large-scale genetics studies: In rare cases, an individual may have a single genetic variation that leads to obesity, but for most obese people, the combined influences of variations in multiple genes likely contribute to excess weight gain. The search for genes that contribute to obesity may be greatly enhanced by the optimal selection of obesity-associated physical, molecular, or behavioral traits (phenotypes) to evaluate. Correlating the presence of an obesity-associated phenotype with a particular genetic variation can help lead scientists to genes that influence obesity. Although BMI, a measure of weight relative to height, has been useful for epidemiologic and other studies, other phenotypes may prove to be even more informative for genetic research. These may include, for example, traits measurable by imaging techniques, molecular analyses, and/or behavioral assessments. A recent NIH-sponsored workshop brought together external experts to recommend methods for measuring various obesity-associated phenotypes that would be practical to implement in a large-scale human genetics study. As a result of this workshop, new initiatives are planned to take advantage of molecular tools in model organisms to expand the list of potential drug targets and to link genetics to pre-obese metabolic states. Longitudinal studies will be needed to connect genes, metabolism and subsequent development of obesity.

Enhancing research on mouse models by facilitating characterization of the mice: The NIH has established a set of centers to provide standardized, high quality metabolic and physiologic analysis of mouse models of obesity, diabetes, diabetic complications, and related disorders.

Breaking the Link Between Obesity and its Associated Health Conditions

Diabetes Prevention Program Outcome Study (DPPOS): The NIH-sponsored Diabetes Prevention Program (DPP) clinical trial examined the effects of lifestyle and medical interventions on the development of type 2 diabetes in over 3,000 adults at high risk for this disease. Upon entering the trial, the participants had elevated blood glucose levels and were overweight. The lifestyle intervention, consisting of modest weight loss and exercise, resulted in a dramatic 58 percent reduced risk of type 2 diabetes in the participants; it was effective in both men and women, and in all of the ages and racial and ethnic groups in the study. The medical intervention, administration of the diabetes drug metformin, caused a lesser but still significant 31 percent reduced risk of developing the disease. The follow-up study to the DPP, the DPPOS, will examine the durability of the lifestyle and medical interventions on weight loss and on the prevention or delay of type 2 diabetes and its cardiovascular complications. The DPPOS will also investigate other associated health conditions in the participants, including, for example, kidney disease and urinary incontinence.

Ancillary studies to the Look AHEAD (Action for Health in Diabetes) clinical trial: This multi-center, NIH-sponsored clinical trial will examine the health effects of an intervention designed to achieve and maintain weight loss over the long term through decreased caloric intake and increased physical activity. Several aspects of the Look AHEAD trial will address diseases associated with obesity. First, the participants being enrolled in the trial are obese patients with type 2 diabetes. Second, the primary health outcome to be assessed is whether or not the intervention affects the development of cardiovascular disease. Third, a number of planned ancillary studies to the trial will investigate other health problems that have been associated with obesity, such as urinary incontinence and fatty liver disease.

Clinical Research Network in Nonalcoholic Steatohepatitis (NASH): This network was recently established by the NIH to accelerate clinical research and progress in understanding NASH, a liver disease that most commonly affects adults who are overweight or have diabetes, insulin resistance, or elevated levels of fat in their blood. The network will establish databases of adults and children with NASH to facilitate research on this disease. Clinical trials are planned to test the effects of an insulin-sensitizing agent or vitamin E, as compared to a placebo, in non-diabetic adult and pediatric participants. In addition, the database will facilitate research on obesity. Because obesity is known to be associated with NASH, ancillary studies are under development to assess the association between obesity and liver disease, as well as on the impact of diet composition or weight change on the course of the disease.

The role of biological factors secreted by fat cells in the development of obesity-associated health conditions: Fat cells produce and secrete a number of biological factors, including, for example, molecules that promote inflammation. The NIH recently convened external scientific experts for a workshop to address the potential roles of fat-cell-derived factors in the development of diseases and other health conditions associated with obesity. The results of this workshop are being considered and should help guide future research toward enhanced understanding of how obesity is linked to its associated health conditions.

Depression associated with obesity and other diseases: Depression complicates the outcomes of interventions for obesity. It may reduce the odds that weight loss will be successful and increases morbidity of conditions associated with obesity, such as type 2 diabetes and heart disease. An ongoing study is evaluating interventions for associated depression and obesity and others are evaluating the utility of antidepressant treatment for conditions such as diabetes.

Weight gain and health problems in children:

The NIH intramural longitudinal study in children is evaluating the relationship between weight gain and insulin resistance, cardiovascular disease risk, and psychosocial dysfunction, including the development of eating disorders.

Pathophysiologic mechanisms of obesity-associated cardiovascular disease: The purpose of this effort is to stimulate novel research approaches to clarify the biologic basis of various obesity-related cardiovascular diseases and disorders, including atherosclerosis, thrombosis, hypertension, cardiomyopathies, heart failure, and arrhythmias/sudden death. Emphasis is placed on basic and clinical mechanistic research that reflects expertise in both obesity and cardiovascular sciences. Areas of high interest in association with cardiovascular disorders include: adipose tissue as a pro-inflammatory and pro-thrombotic endocrine organ; lipid infiltration (lipotoxicity) in non-adipose tissues and organs; maladaptation of the cardiovascular, endocrine, and neural systems in obesity; and the impact of obesity on the maturation of the cardiovascular system in young animals.

Coronary Artery Risk Development in Young Adults (CARDIA) Study: This study examines the development of subclinical cardiovascular disease (CVD) in 5,115 African American and white men and women, ages 18-30 years at entry, from a wide range of educational levels. The original goal of the study was to identify the determinants of major CVD risk factors, particularly obesity, hypertension, and hyperlipidemia, during the critical years of young adulthood. There have been striking increases in obesity among CARDIA participants over 15 years—from 6 percent to 25 percent in whites and 11 percent to 37 percent in African Americans. Body Mass Index (BMI) increases were greatest at the upper ranges of BMI with large weight gains more common among those already overweight

at baseline. A second aim of CARDIA is to examine the role of interactions between genetic and environmental factors in the development of CVD and its risk factors, including obesity. An ongoing ancillary study to CARDIA is examining: 1) the role of visceral fat independent of total fat in risk of developing other CVD risk factors, including type 2 diabetes, and 2) race-gender differences in resting energy expenditure and its relationship to adiposity.

Framingham Heart Study: This is a longitudinal investigation of physiological, environmental, and genetic factors influencing the development of cardiovascular disease in over 14,000 men and women in three generations. Multiple measures of weight, height, girth and selected measures of skinfold thickness have been performed. Of major interest in the future is to identify genetic determinants of obesity and changes in BMI over time, as well as environmental modifiers of putative obesity genes.

Genetics of Coronary Artery Disease in Alaska Natives (GOCADAN): GOCADAN is a study of approximately 40 Alaska Native families comprising 1,200 family members ages 18 years and older. Preliminary data indicate obesity is rising but is not yet as prevalent among Alaska Natives as it is among American Indians in the contiguous 48 states. Analyses will focus on genetic and environmental contributors to obesity. The contribution of changing dietary and physical activity patterns as well as seasonal patterns will also be investigated. Heritability estimates and linkage analyses to identify obesity-related genes are planned.

Strong Heart Study and Strong Heart Family Study:

These studies were initiated to estimate levels of cardiovascular disease risk factors in 4,500 American Indian men and women ages 45 to 74 and their families from three geographically diverse centers. The prevalence of overweight and obesity in these communities is among the highest in the world. More recently a family study of all family members ages 15 years and older has been initiated, which will include 3,600 participants belonging to approximately 120 families. Heritability estimates and linkage analyses to identify obesity-related genes are planned when data collection is complete.

Multi-Ethnic Study of Atherosclerosis (MESA):

This research investigates the prevalence, correlates, and progression of subclinical cardiovascular disease (CVD) in a population-based sample of 6,800 men and women ages 45 to 84. Thirty-eight percent of the cohort is white, 28 percent African American, 22 percent Hispanic, and 12 percent is Asian (Chinese), recruited from six field centers. Four clinical examinations are planned over a 7-year period. Participants will be followed for identification and characterization of CVD events and interventions received. MESA will address the role of obesity in the development and progression of subclinical CVD.

Atherosclerosis Risk in Communities Study (ARIC):

This study is a large-scale, long-term program that measures associations of established and suspected coronary heart disease (CHD) risk factors with both atherosclerosis and new CHD events in 15,800 men and women from four diverse communities. The ARIC study has measured height, weight, girth, and other obesity measurements during the 4 examinations. Analyses have often used BMI as an important covariate in predicting CHD or understanding the role of obesity in the occurrence of carotid atherosclerosis. Recent analyses have shown that weight loss associated with ill health is associated with increases in short-term mortality in the subsequent 4 years; that weight gain is associated with increased incidence of hypertension and increased levels of blood pressure; and that all measures of obesity studied (BMI, waist-to-hip ratio, and waist circumference) were related to the incidence of type 2 diabetes, but the waist measure had slightly better predictability. Follow-up of the cohort for CHD events is ongoing.

Cardiovascular Health Study (CHS): This population-based longitudinal study investigates risk factors for the development of coronary heart disease (CHD) and stroke in 5,888 men and women ages 65 and older. Analyses in CHS have demonstrated that obesity is associated with impaired fibrinolysis and with higher circulating levels of inflammatory markers, factors that have been related to greater risk of CVD. CHS has shown that high body fatness is an independent predictor of disability in the elderly. CHS investigators are developing improved methods to diagnose left ventricular hypertrophy by electrocardiogram in overweight as well as normal weight subjects. Through continued follow-up and analysis of stored samples, researchers are examining the impact of inflammatory and genetic factors on weight change in the elderly, and the importance of weight change in predicting morbidity, disability, and mortality.

Jackson Heart Study (JHS): This prospective study examines the environmental and genetic factors influencing the development of CVD in 6,500 African Americans ages 35 to 84 residing in Jackson, Mississippi. Specific study objectives are to determine the roles of CVD risk factors such as obesity, dyslipidemia, insulin resistance, and hypertension, in the development and progression of CVD in African Americans, with emphasis on hypertension-related disease (left ventricular hypertrophy, congestive heart failure (CHF), CHD, stroke and renovascular disease). The prevalence of obesity is increasing nationwide, and is especially high in Mississippi.

Insulin Resistance and Atherosclerosis Study (IRAS) and IRAS Family Study: These studies are designed to identify the genetic basis of insulin resistance and visceral adiposity as intermediate components in the pathways leading to atherosclerosis and type 2 diabetes. The IRAS Family Study will determine whether insulin resistance and abdominal fat cluster in families and whether specific genes influence these traits. Investigators are exploring the extent to which behaviors such as diet, physical activity, and smoking influence insulin resistance and abdominal obesity. Analyses are focusing on whether the relationship between abdominal adiposity and insulin resistance is independent of overall body mass; whether the relationship differs by ethnicity, gender, or body mass; and whether type of fat deposit is more strongly associated with insulin resistance and insulin secretion. Other analyses have evaluated whether fat-patterning profiles, as measured by computed tomography, differ between relatives of diabetic and nondiabetic probands. Preliminary analyses support the hypothesis that adiposity and diabetes may be common components of a larger heritable syndrome, but they do not support previous suggestions that the early defects in adipose tissue are manifested primarily in visceral tissues.

The NHLBI Family Heart Study: This study was designed to identify and evaluate genetic and environmental determinants of coronary heart disease (CHD), atherosclerosis and CVD risk factors. Clinical examination and follow-up were conducted on a total of 1,253 families including 5,975 individuals. Analyses from this study provide evidence for a recessive major gene as well as other multifactorial background factors influencing BMI, and suggest that the frequencies of these factors, one of which appears to be genetic, may vary among diverse populations in the United States. Research activities are still ongoing.

The Family Heart Study—Subclinical Atherosclerosis Network (FHS-SCAN): This study is intended to identify genetic factors that increase susceptibility to: 1) coronary and aortic atherosclerosis and 2) inter-individual variability in the inflammatory response. The study plans to enroll 401 informative pedigrees (3,027 individuals) previously examined and genotyped by the NHLBI Family Heart Study, to quantify coronary and aortic calcium, and to identify genes associated with atherosclerosis. The extensive metabolic, behavioral, and environmental data already collected on these pedigrees and sibships, as well as a *de novo* assessment of the inter-individual variability in the inflammatory burden and host response, will be available to enhance phenotypic homogeneity and increase analytic power in assessing the genetic basis of atherosclerosis. Anthropometric data including height, weight, and waist and hip circumference will be used in future analyses on the relationship of BMI to coronary calcium.

HERITAGE Family Study: This study is designed to study the role of the genetic and non-genetic factors in cardiovascular, metabolic and hormonal responses to aerobic endurance exercise training and the contribution of regular exercise to changes in CVD and diabetes risk factors. Participants were previously sedentary but free of significant medical conditions and diseases before embarking on a standardized 20-week stationary bicycle exercise-training program. Completing the program were 483 Caucasians from 99 families and 259 African Americans from 105 families. Anthropometric, cardiovascular, and metabolic responses to submaximal and maximal exercise, demographic and behavioral variables were measured before and after training. Whereas total adiposity, subcutaneous fat and visceral adipose tissue were characterized by strong familial aggregation in HERITAGE, the changes brought about by regular exercise were characterized by more complex patterns of familial resemblance. Genomic scans have allowed identification of several chromosomal regions harboring genes linked with the exercise-induced changes in total adiposity and abdominal fat as well as in blood pressure, lipoproteins and glucose and insulin metabolism. Numerous candidate genes have been investigated. Sequence variations in adrenergic receptor genes; the genes for the glucocorticoid receptor, leptin receptor, angiotensinogen, and angiotensin converting enzyme; and other genes have been shown to be associated with adiposity phenotypes or components of the metabolic syndrome.

Dose-Response to Exercise in Women (DREW):

The primary goal of this study is to investigate the effects of different amounts of exercise on both cardiorespiratory fitness and risk factors for CVD in women 45 to 75 years of age. A total of 450 sedentary, overweight or obese, postmenopausal women are randomly assigned to groups that will exercise at energy expenditures that represent the consensus public health recommendations for physical activity (8 kcal/kg/week by the U.S. Public Health Service, American Heart Association, and American College of Sports Medicine) and at doses 50 percent above (12 kcal/kg/week), and 50 percent below (4 kcal/kg/week). Physical activity is performed at moderate-intensity for all participants, with the amount of time varying to achieve the different doses of exercise. Outcomes include measurement of CVD risk factors, psychosocial variables, health-related quality of life, body composition, and body fat distribution. This research will provide information about the characteristics of sedentary women who are most likely to benefit from various exercise doses and what level of exercise, if any, has any health benefit.

Women's Health Initiative (WHI): WHI is a very large multi-site research program whose purpose is development of strategies for preventing heart disease, breast and colorectal cancer and osteoporosis in postmenopausal women. The study has several separate protocols. Obesity is an important secondary focus of the WHI. Because about one-third of WHI participants are obese, and another one-third are overweight, the study can contribute important information on the health effects of obesity and ways of controlling obesity. In the trial of low-fat dietary pattern (high in fruits, vegetables, and grains, and therefore high in carbohydrates) involving over 48,000 older women, modest weight reduction compared to the control group was observed in the first few years, with some persistent but smaller

difference in later years. In the trials of hormone therapy involving over 27,000 women, obesity appears to have modulated the effects of hormones on fractures (less benefit). In contrast to concerns that the hormone combination estrogen plus progestin may increase obesity, the trial results showed a significant reduction in abdominal obesity in the hormone group compared to the placebo group. This reduction was accompanied by a reduction in insulin resistance, indicated by significant reductions in fasting serum insulin and glucose. The ongoing observational study of over 93,000 women also provides opportunities for study of the relationship of baseline obesity, and changes in adiposity, to health outcomes.

Health, Eating, Activity, Lifestyle (HEAL) and Breast Cancer Prognosis Study: This study is designed to look at the associations among physical activity, eating habits, weight patterns, diet, hormones, and prognostic factors for breast cancer in a multi-ethnic cohort of breast cancer survivors. Because each of the study sites draws from a distinct racial and ethnic population mix, the investigators will have a unique opportunity to examine the differences in these associations among whites, Hispanics, and African Americans. Of particular interest is the interplay of these lifestyle factors because women who are overweight or obese have a poorer survival and increased breast cancer recurrence rate compared with lighter-weight women. Overweight, obesity, and adult weight gain also are risk factors for postmenopausal breast cancer. Women with breast cancer are at particularly high risk of developing new primary, recurrent, disseminated, or fatal breast cancer. To date, women with breast cancer have had few options, aside from Tamoxifen therapy, to reduce this risk in the long-term. By identifying prognostic factors, researchers can develop prevention strategies to prevent new or recurrent disease and to prolong survival with high quality of life.

Epidemiologic research addressing obesity and cancer: A large number of NIH-supported studies are focusing on the influence of obesity and physical inactivity on different types of cancers. Several examples include: the Breast Cancer Detection Demonstration Project (BCDDP) Follow-up Study and other breast-cancer related studies; the Framingham Heart Study, which has a cancer component; a study of bone mineral density and cancer risk; the NIH-AARP Diet and Health Study, which examines nutrition in relation to major cancers among over half a million men and women in the U.S.; a study of physical activity, diet, body weight and composition in relation to plasma markers of cancer risk among Chinese adults (in Shanghai); the CONCeRN Study, which is an investigation of colorectal adenoma prevalence among asymptomatic women at U.S. Naval hospitals undergoing complete colonoscopy; and the Cohort Consortium, which is a new effort that combines several prospective cohort studies from around the world and provides information on energy balance-related factors as well as biologic specimens for environment-gene interaction research. Researchers are also examining factors relevant to obesity in participants of several cancer-related clinical trials, including the Alpha-Tocopherol Beta-Carotene (ATBC) Study, a prospective cohort study of Finnish male smokers; the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial (with a focus on ovarian and prostate cancers); and the Polyp Prevention Trial. Other studies relate to biliary tract cancers, renal (kidney) cancer, digestive tract cancer, and esophageal and gastric cardia adenocarcinoma.

Cross-cutting Topics

Health Disparities—Addressing the Needs of Specific Populations

Research efforts addressing the needs of specific populations, such as children and racial/ethnic minorities, are found throughout the Strategic Plan document, because these efforts are integral and critical to research in the many scientific areas addressed by the Plan, as well as to the education and outreach activities described in the Plan for disseminating the results of research to the public and healthcare providers.

Enabling Technologies

Oxygen-18, a resource for measuring energy expenditure: Oxygen-18 is a form of oxygen that is used for several biomedical applications; importantly, when incorporated into water, it can be used to measure energy expenditure in animals and humans. However, current suppliers of oxygen-18 have been unable to meet increased worldwide demand, resulting in shortages for the past several years that have disrupted and delayed research projects. To address this problem, the NIH is currently working with the Department of Energy to explore ways to increase production of oxygen-18 for use in research.

Improving diet and physical activity assessment:

Research related to body weight often requires assessments of dietary intake and physical activity, yet current methods are not ideal. Thus, the NIH has launched a new effort to encourage research to improve existing instruments used for measuring dietary intake and physical activity in populations over time, to develop or refine new technologies for such measurements, and to improve statistical and analytical techniques used in the evaluation of diet and physical activity measurements.

National Food and Nutrient Analysis Program

(NFNAP): This Program is a trans-governmental inter-agency agreement between the USDA, the NIH, and other HHS agencies, which ensures the availability of current and accurate information on the nutrient content of commonly eaten foods in the U.S. One thousand foods accounting for the majority of Americans' nutrient intake are being sampled according to a population-weighted stratified plan and are analyzed directly for over 100 key nutrients. The resulting data are accurate, up-to-date, and statistically representative of national food consumption patterns. Data also are being collected to estimate the variability of the content of important nutrients in selected foods. The new NFNAP results will replace older data that do not reflect current food formulations, and for many foods and food constituents will be the first composition data ever available. The research results are made available to researchers and the public through the USDA National Nutrient Databank. NFNAP data are a critical resource for developing dietary guidance and evaluating the energy, macronutrient, and micronutrient content of diets. The sampling and analysis plan includes the determination of nutrient content for an array of commonly eaten "fast foods." The energy density, nutrient density, and fiber content of individual foods and total diets also can be derived from NFNAP data; this is key information for assisting individuals in planning diets that will foster either weight loss or maintenance of healthy weight, as appropriate.

Multidisciplinary and Interdisciplinary Research Teams

Multidisciplinary research and the CNRU/ONRC program: As discussed, the CNRU/ONRC program is designed to encourage multidisciplinary research that encompasses obesity and many related health conditions, including diabetes, cardiovascular disease, cancer, and other diseases.

Training of Investigators

The Nutrition Academic Award program: Physicians and other healthcare providers are in an ideal position to counsel patients about optimal nutrition for the prevention and treatment of disease, yet only 22 percent of U.S. medical schools offer required courses in nutrition. To improve this situation, the NIH is supporting the Nutrition Academic Award program. A total of 21 U.S. medical schools have received awards to enhance their curricula in order to increase nutrition knowledge and improve clinical practice skills of medical students, other health professions students, and practicing physicians. These medical schools are developing, implementing, and evaluating comprehensive nutrition education models that emphasize prevention and treatment of cardiovascular diseases, obesity, hypertension, diabetes, and other chronic diseases. Topics include physical activity, energy balance, and nutrition throughout the lifespan (e.g., pediatrics, young adulthood, women's health, aging). Curriculum materials (guidelines, other teaching tools, and assessment tools) developed with program funds have been disseminated to other medical and health professional schools. In addition to this program, other efforts are under way to educate physicians, dietitians and nurses on the health risks associated with obesity as well as the recommendations on treatment options; see, for example, the Education/Outreach and Translation Efforts section of this Appendix.

Outcomes Research Working Group: Outcomes research is defined as applied clinical research that generates knowledge to improve clinical decision-making and healthcare delivery to optimize patient outcomes. A workshop was held to explore the potential for advances in knowledge about the treatment and prevention of cardiovascular disease through clinical research and to identify directions for future activities in cardiovascular disease outcomes research.

Molecular and cellular basis of cardiovascular disease training focused on lipoprotein metabolism and obesity: The NIH is providing research career development training in a multidisciplinary research environment with a focus on areas such as lipoprotein metabolism and obesity, muscle differentiation and function, developmental biology, vascular biology, and genetics.

CNRU/ONRC Program: As noted, one aspect of the CNRU/ONRC Centers program is to strengthen training environments for medical students, physicians, and other health personnel and staff.

Education/Outreach and Translation Efforts

WIN and OEI — complementary education and information efforts of the NIH: The Weight-control Information Network (WIN) of the NIDDK and the NHLBI Obesity Education Initiative (OEI) both strive to disseminate informational and educational messages and materials. Through the complementary and coordinated efforts of both programs, an increased number of healthcare professionals, patients, and a variety of public audiences are likely to hear the messages on overweight and obesity and associated diseases. Both WIN and the OEI work not to duplicate efforts, but rather to enhance each other's public and professional outreach activities. These programs are described in further detail elsewhere in this Appendix.

The Weight-control Information Network (WIN) of the NIDDK: WIN will continue providing health professionals and consumers with science-based information on obesity, weight control, physical activity, and nutrition. This information includes, for example, fact sheets and brochures for the public as well as *WIN Notes*, a quarterly newsletter for health professionals and consumers. WIN has recently launched several new outreach activities. For example, WIN has begun a new project to promote the distribution, by healthcare providers, of its new series of booklets in English and Spanish on "Healthy Eating and Physical Activity Across Your Life Span." This series contains booklets targeted to different populations of the public, including "tips for adults," "tips for older adults," "tips for parents," and "tips for pregnancy." The new outreach project relating to these booklets will involve communications to physicians, dietitians, and community health centers, including African American and Hispanic healthcare professionals and community healthcare centers that serve predominantly Hispanic populations. In addition to the different age groups addressed by the series of booklets noted above, a guide booklet for teenagers has also been developed.

"Sisters Together: Move More, Eat Better":

This program, developed by WIN, encourages African American women to maintain a healthy weight by becoming more physically active and eating healthier foods. WIN has begun a new outreach effort to contact historically Black colleges and universities (HBCU), hair and nail salons, and churches nationwide to promote the availability of "Sisters Together" brochures.

"Small Steps. Big Rewards. Prevent Type 2

Diabetes:" This educational campaign emphasizes the significant health benefits of moderate weight loss and exercise. *Small Steps. Big Rewards.* strives to disseminate the dramatic results of the lifestyle intervention used in the Diabetes Prevention Program (DPP) clinical trial. Supported by the NIH, the DPP demonstrated that the onset of type 2 diabetes, a disease for which obesity is a strong risk factor, could be prevented or delayed in people at high risk through moderate weight loss—5 to 7 percent of body weight—and moderate exercise—150 minutes of physical activity weekly, such as brisk walking on most days of the week. The finding that moderate weight loss and activity can have significant health benefits is the key message of the campaign, which includes a toolkit for healthcare providers and materials for people at risk for this obesity-associated disease. The campaign is run by the National Diabetes Education Program (NDEP), which is a partnership of the NIH, the CDC, and over 200 public and private organizations.

The NHLBI Obesity Education Initiative (OEI):

Since 1991, the OEI has been working to enhance research dissemination and education activities that address the increasing prevalence of overweight and obesity in the population. The OEI utilizes a three-pronged outreach approach directed at health professionals, patients and the public, and entire communities to deal with the increasing public health problem of overweight and obesity. Because of the association of obesity and physical inactivity with the various risk factors for CVD and impaired lung function, the OEI has enhanced and integrated education activities related to both weight and physical activity across NHLBI's other national education program areas. For example, the release of the *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: Evidence Report* involved the endorsement of 52 professional societies, government agencies and consumer groups represented on the Coordinating Committees of the National High Blood Pressure Education Program (NHBPEP) and the National Cholesterol Education Program (NCEP) as well as the North American Association for the Study of Obesity (NAASO), and an advisory group of external experts associated with the NIDDK. The NCEP and the NHBPEP include messages about the health risk associated with overweight and obesity in both professional and public education materials. The recommendations about weight loss in adults from the Obesity Clinical Guidelines were also considered by the NCEP and NHBPEP expert panels that developed the 3rd Adult Treatment Panel Report on cholesterol and the JNC VII report on hypertension, respectively.

Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: Evidence Report:

Since the release of these guidelines, a number of professional products and activities have been developed, implemented, and broadly disseminated. Development and dissemination efforts include working with a number of professional societies including the North American Association for the Study of Obesity (NAASO), the American Dietetic Association, and the American Medical Association to encourage healthcare practitioners to appropriately treat their overweight and obese patients by providing them with the necessary practical tools and strategies. The OEI has also worked with CenterNet, Cine-Med, NAASO, and the Centers for Obesity Research and Education (CORE) to provide training and continuing medical education (CME) credits to physicians, dietitians and nurses based on the Clinical Guidelines. CenterNet is an innovative network that resulted from the collaboration between HealthCare Management Television and the Association of Academic Health Centers. The CME programs are widely marketed. Additionally, a Practical Guide for physicians and other healthcare providers has been developed.

The "Aim for a Healthy Weight" Web page: This NIH web page has both "Information for Health Professionals" that includes the Clinical Guidelines, and "Information for Patients and the Public" that contains a BMI calculator, food shopping and preparation tips, dining out ideas, low-calorie menu plans, physical activity ideas, and other information. The Web page includes an interactive quiz on "Portion Distortion" that illustrates the change over the past 20 years in the portion size of different foods being offered for sale to the public in restaurants, supermarkets, or other food outlets.

Hearts N' Parks: This nationwide, community-based program, supported by the NHLBI OEI in collaboration with the National Recreation and Park Association (NRPA), is aimed at reducing overweight and obesity by encouraging a heart healthy eating plan and increased physical activity. Fifty Magnet Center sites have been created to implement Hearts N' Parks activities in high-risk communities in Indiana/Ohio, Illinois, Georgia, Missouri, Michigan, Florida, Maryland, Nevada, and New Mexico. Six additional Marine Corps bases serve as another Magnet Center site. A Hearts N' Parks Community Mobilization Guide has been developed to focus on the 5 Ps of Hearts N' Parks, namely People, Programs and practices, Public visibility, Partners, and Performance measures. The Guide and its accompanying videotape have been distributed to 1,400 interested park and recreation departments, clinics, and State health departments. All Hearts N' Parks sites have specific responsibilities for 3 years that include implementing heart healthy programs for youth and adults, creating partnerships, and collecting performance data on program participants, as well as information about personnel and facilities. To date all sites are utilizing the Child and Adolescent Trial on Cardiovascular Health (CATCH) Recreation resource that provides approximately 300 noncompetitive physical activities appropriate for elementary school age children and is adapted from the NIH-funded study. Many of the sites have received local, State, or national visibility for their programs.

Memorandum of understanding aimed at improving health: The NIH has joined other Federal agencies of HHS to sign a memorandum of understanding (MOU) with NRPA to attempt to improve public health by encouraging physical activity and healthy eating; to create community programs for children, seniors and families; and to remove environmental barriers to physical activity such as those for the disabled. The participating government agencies include the NIH, the Centers for Disease Control and Prevention, and the President's Council on Physical Fitness and Sports as well as the HHS Office of Disease Prevention and Health Promotion (ODPHP).

The CVD Enhanced Dissemination and Utilization Centers (EDUCs): These centers stimulate partnerships to improve cardiovascular health in communities at highest risk for CVD (cardiovascular disease). One example is the St. Mary's Hospital EDUC in Huntington, West Virginia, which is working with 8,000 elementary school children, their families, and school staff in 35 public schools in Appalachia to screen them for CVD risk factors and then implement healthy lifestyle changes. They have successfully implemented a walking program for students, who have logged 10,000 miles in the last year. In addition, they screened 1,235 third and fourth graders for CVD risk factors and referred those at high risk to clinics for more testing. Twenty-six percent of third graders and 25 percent of fourth graders were overweight. About 35 percent of both third and fourth graders were found to have high blood pressure, and about half of them had borderline or high blood cholesterol. The West Virginia Health Right EDUC in Charleston, West Virginia, is providing education on physical activity, nutrition/healthy cooking, and weight loss to uninsured and under-insured patients at the free clinic. This EDUC uncovered high risk factor burden: about two-thirds of the patients had three or more CVD risk factors (high blood cholesterol, overweight, high blood pressure, diabetes or smoking).

The University of North Texas EDUC is using NIH's "Salud para su Corazón" materials to train lay health educators to work in the community and teach heart healthy eating skills and encourage physical activity. New CVD EDUCs include the Baltimore City Housing Authority, which will train community health workers to educate residents in public housing projects about heart healthy nutrition and physical activity, and environmental change activities in grocery stores, restaurants, and schools. The Wright State University EDUC in Ohio is implementing health systems change and quality assurance interventions aimed at improving patient outcomes related to control of high blood pressure and high blood cholesterol and reducing overweight/obesity. Other CVD EDUCs in Nebraska, North Carolina, and Ohio will also focus on reaching high risk populations through community-based education and skill-building activities as well as nutrition and environmental change programs.

U.S.-Mexico Border States Cardiovascular Health Outreach: An interagency agreement between the NIH and the Health Resources and Services Administration is funding and participating in the training of lay health educators to conduct family health education and encourage physical activity in extremely low-SES (socio-economic status) communities in Texas, New Mexico, Arizona, and California.

The NIH-Indian Health Service (IHS) Partnership To Strengthen the Heartbeat of Native Americans and Alaska Natives: This partnership began by working with 4,000 members of the Pueblo of Laguna, New Mexico, 2,500 members of the Ponca Tribe of Oklahoma, and 32 villages of the Bristol Bay Area Health Corporation in Alaska to implement a train-the-trainer program and establish a cadre of community heart health educators. The project has worked so well that a National Training Workshop was planned that included representatives from all IHS and local tribal service units. In addition, key national, regional, and local decision makers who can advocate for

cardiovascular health in American Indian/Alaska Native communities will participate. The workshop was designed to facilitate both interaction and engagement. The community health representatives, nurses, and dietitians taught adults about heart healthy nutrition and the importance of regular physical activity.

Efforts focused on Asian and Pacific Islander populations: Other community efforts include working with the Filipino and Vietnamese communities to develop fact sheets on cardiovascular disease risk factor prevention including nutrition and physical activity, and a collaboration with the Molika'i General Hospital in Hawaii to implement a transgenerational approach to heart health that calls upon the wisdom and reverence of the kupuna (elders) to work with teachers who will be trained to conduct the heart-health sessions for children. A culturally competent heart health training manual, "Healing our hearts, healing our families," is being developed as well as a related elementary school curriculum for native Hawaiian children. Because overweight and obesity are related to heart health, the various fact sheets and curricula encourage healthy eating habits, increased physical activity, and the need to watch portion size and manage weight in addition to lowering high blood pressure and cholesterol.

The NHLBI OEI Healthy Weight Initiative: This national outreach initiative includes communications products and activities, as well as community outreach activities that meet the public education goals of implementing the NHLBI's national health education action plan on reducing overweight/obesity and on promoting a healthy weight. The current outreach effort will seek to increase the level of awareness of community organizations, especially those involved in parks and recreation, and the public, particularly those at high risk, about the increased risks associated with overweight and obesity and the health benefits of maintaining a healthy weight. It will also explore the potential role of environmental change in a community setting in helping individuals achieve a healthy weight.

"5 A Day for Better Health:" This campaign has incorporated messages on the importance of maintaining a healthy weight and a physically active lifestyle as an effort to encourage public awareness of these health issues. These messages are a key component of a recent campaign focused on increasing African American men's consumption of fruits and vegetables.

NIH participation in inter-departmental efforts regarding the Food Guide Pyramid: The Food Guide Pyramid is one of several tools used to help provide nutrition education to the American people, and it is intended to help convey how a person should select a diet consistent with the recommendations within the U.S. *Dietary Guidelines for Americans*. (The *Dietary Guidelines for Americans* is the document that is used to set dietary guidance policy.) Although developed by the United States Department of Agriculture (USDA), the Food Guide Pyramid is now considered a joint document of the USDA and the Department of Health and Human Services. The NIH is currently coordinating efforts with the USDA concerning a revision of the Food Guide Pyramid via several actions, primarily through the NIH Division of Nutrition Research Coordination (DNRC) and its NIH Nutrition Coordinating Committee (NCC). The NIH has taken a strong position in emphasizing the need for scientific fact to serve as the basis for dietary recommendations.

Translational research: The NIH is currently assessing the results of a recent conference on bringing successful findings from diabetes and obesity research to the public. The results of this conference will help chart future directions on such issues as the design of effective translational research interventions. Research on the translation of new science to patient care is also the focus of an ongoing effort launched by the NIH in collaboration with the Agency for Healthcare Research and Quality, the CDC, and the American Diabetes Association.

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Office of Research on Women's Health

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* Dr. Gansheroff had major responsibility for compiling this document.

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Front Cover — Image Credits:

Clockwise from top right:

Mice (lean and obese): The Jackson Laboratory.

Child kicking soccer ball: NIDDK Weight-control Information Network (WIN)
(from the publication “Cómo Alimentarse y Mantenerse Activo Durante Toda La Vida — Cómo ayudar a su hijo”).

Structure of the leptin molecule: Dr. Faming Zhang, Lilly Research Laboratories.

Three children eating: Indian Health Service.

Scientist: Getty Images.

Family at meal: Getty Images.

Couple walking: Corbis.

Center image: Morton GJ, Alkire G, and MW Schwartz, Harborview Medical Center and University of Washington.