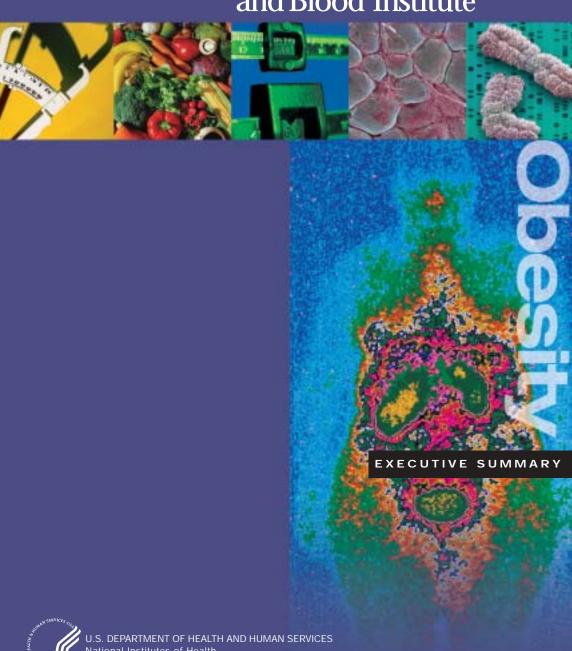
THINK TANK ON

# Enhancing Obesity Research at the National Heart, Lung, and Blood Institute



National Heart, Lung, and Blood Institute

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EXECUTIVE SUMMARY



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES National Institutes of Health National Heart, Lung, and Blood Institute

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As a Nation, we are confronted with an unprecedented obesity epidemic—the solution to which will be as complex in its nature as the epidemic itself. An obesity epidemic, as well as the dramatic parallel increase in associated comorbidities such as heart disease, diabetes. and asthma can be considered nothing less than an expanding public health crisis. So troubling is this crisis to the health and well-being of the American public that the Secretary of the U.S. Department of Health and Human Services (DHHS) considers it a health care priority. We at the National Institutes of Health (NIH) share this significant concern and have joined together to emphasize the importance of employing solid science to support the development of new interventions and treatments. In fact, the NIH has undertaken a series of specific activities to see how the Institutes can address important issues relevant to the obesity epidemic.

The obesity epidemic together with the relationship of obesity to the growing population burden of chronic disease presents unprecedented research opportunities and challenges. But we also are mandated to develop timely and effective solutions. Herein lies the challenge. Decades of obesity-related research funded by the National Heart, Lung, and Blood Institute (NHLBI) and throughout NIH have yielded many important discoveries about both etiological pathways and preventive or therapeutic interventions. Yet, there is a sense that the problem is outpacing these research efforts.

In the spring of 2003, Dr. Claude Lenfant, Director, NHLBI, convened a Think Tank that included many renowned experts in obesity research and asked participants for their best thinking about what targeted research recommendations would be most effective in confronting this public health challenge. The results of their deliberations are provided in this report.

On behalf of the NHLBI, I want to thank the many scientists, clinicians, and advocates from across the country who gave generously of their time and knowledge and without whom this report would not have been possible. I am grateful especially to Dr. Claude Bouchard and Dr. Shiriki Kumanyika for serving as cochairs of the meeting. This report reflects their dedication and the great amount of their personal time and energy dedicated to this effort.

We hope that the report will stimulate new ideas for further investigation as well as creation of innovative collaborations—by researchers, by government agencies, by public/private partnerships—to address this challenging public health crisis.

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# Obesity— The Unchecked Epidemic

Overweight and obesity affect all segments of our population, and their prevalence continues to increase at an alarming rate—today, two out of three Americans are considered overweight or obese. The epidemic of obesity —together with the relationship of obesity to the population's burden of heart, lung, blood, and other diseases—presents unprecedented research opportunities and challenges. Enhanced research to accelerate knowledge is the key to unraveling the etiologies and providing interventions that will counteract this growing public health crisis.

In March 2003, the National Heart, Lung, and Blood Institute (NHLBI) convened a 2-day *Think Tank on Enhancing Obesity Research at the NHLBI*, which brought together a diverse group of stakeholders from the academic, consumer, and professional communities, including:

- Basic biological and behavioral obesity researchers who view the current epidemic as a challenge for understanding the etiology and pathological processes of this all-too-common condition,
- Basic researchers who study cardiovascular, pulmonary, and blood diseases and sleep disorders and for whom the increase in obesity provides a well-defined focal point for the study of pathogenesis,
- Clinical researchers—interventionists who have witnessed the tremendous increase in the demand for their services as the number of obese people increases and whose efforts have been plagued by the difficulty of achieving long-term success,
- Clinical researchers—observational epidemiologists who examine relationships between factors associated

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- with obesity as well as the relationship between obesity and health problems,
- Public health researchers for whom the obesity epidemic constitutes a mandate to discover immediate ways to turn off the flow of obesity-promoting influences in the society at large, and
- Representatives of the various consumer and professional constituencies who are experiencing the effects of the obesity epidemic in their communities and are looking for practical ways to alleviate it.

## Obesity and Its Relevance to Heart, Lung, and Blood Diseases and Sleep Disorders

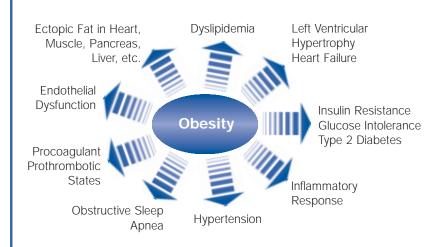
The growing epidemic of obesity is of particular relevance to NHLBI because of the clearly documented associations of obesity with a number of cardiovascular (CVD) and pulmonary disease risk factors and outcomes, including mortality rates and unfavorable risk profiles. An essential part of the public health solution is research to increase our understanding of obesity and its etiology, as well as possible treatments for obesity and its comorbidities. The Think Tank participants made recommendations designed to enhance the Institute's research portfolio. They targeted key areas linking obesity research to the emerging broader spectrum of research needs including metabolic syndrome, CVD, heart failure (HF), asthma, hypertension, and dyslipidemia. These recommendations are summarized by topic in this executive summary.

#### Cardiovascular Disease

As illustrated in Figure 1, obesity is associated with CVD, and the relationship may only be partly via established risk factors. In other words, the totality of the reasons obesity affects CVD remains to be established.

CVD imposes a large morbidity, mortality, and economic burden on individuals, families, and the Nation. Common

### **Obesity and Cardiovascular Risk**



Adapted from Sharma, 2002. Source: Reprinted with permission from Nature Publishing Group © (Sharma, AM. Adipose tissue: a mediator of cardiovascular risk. *International Journal of Obesity and Related Metabolic Disorders* 2002;26:S6, figure 3).

forms are atherosclerosis, hypertension, chronic obstructive pulmonary disease, and blood-clotting disorders. The most serious atherosclerotic diseases are coronary heart disease (CHD), as manifested by heart attack and angina pectoris, and cerebrovascular disease, as manifested by stroke. Mortality rates from CHD are higher for obese than for nonobese adults. Recently, considerable attention has been devoted to adipose tissue pathophysiology associated with CVD. In obese persons, the amount of lipid stored in the adipose organ is substantially increased. So is the rate of free fatty acid release, even under basal conditions, at least in part as a result of the diminished inhibitory effects of insulin on lipolysis. Whether the higher free fatty acid flux in the peripheral circulation and the increased availability of free fatty acids to organs and tissues play a role in the increased CVD risk

associated with obesity remain controversial issues that warrant further investigation. Ectopic deposition of lipid in heart muscle recently has been shown to have unfavorable functional consequences. A better understanding of the mechanisms by which low HDL-cholesterol levels develop in conjunction with increased adiposity, and of how low HDL relates to the augmented cardiovascular morbidity and mortality rates in obese people would increase the knowledge base regarding primary and secondary prevention.

# Hypertension and Hemodynamic Disturbances

Obesity is associated with a greater risk that an individual will develop hypertension. Children and adults with obesity have, on average, higher systolic and diastolic blood pressure than normal-weight children and adults. However, the mechanisms that link obesity to hemodynamic disturbances are poorly understood. Research is needed to elucidate why some obese people become hypertensive while others do not. Such knowledge could translate into better risk identification and treatment strategies.

# Metabolic Syndrome and Its Constellation of Risk Factors

The prevalence of metabolic syndrome is increasing at a disturbing rate and parallels the obesity epidemic. The metabolic syndrome is identified by the presence of three or more of the components listed in Table 1. Other risk factors that may present with the metabolic syndrome include atherogenic dyslipidemia, elevated blood pressure, insulin resistance (with or without hyperglycemia), a prothrombotic state, and a proinflammatory state. Evidence indicates that obesity contributes to each of these risk factors; however, the strength of the evidence varies and the mechanisms involved are not well understood. Research on the role of a sedentary lifestyle as a cause or as a permissive factor in the development of the metabolic

Clinical Identification of the Metabolic Syndrome (NCEP, 2002).

Risk Factor	Defining Level
Abdominal Obesity Men Women	Waist Circumference* >102 cm (>40 in) >88 cm (>35 in)
Triglycerides	≥150 mg/dL
HDL cholesterol Men Women	<40 mg/dL <50 mg/dL
Blood pressure	≥130/85 mmHg
Fasting glucose	≥110 mg/dL

<sup>\*</sup>Some male persons can develop multiple metabolic risk factors when the waist circumference is only marginally increased, e.g., 94–102 cm (37–39 in). Such persons may have a strong genetic contribution to insulin resistance. They should benefit from changes in life habits, similarly to men with categorical increases in waist circumference.

syndrome and on differences between men and women in different ethnic groups at various phases of life also is needed. Determining whether a premetabolic syndrome can be recognized in children and young adults is important and could lead to earlier identification and prevention of disease progression. It is imperative to acquire a better understanding of any predictive targets that would allow early intervention and thus prevention of future cardiovascular events.

#### **Heart Mass and Heart Failure**

Mortality rates from heart failure (HF) increase as a function of body mass index (BMI). Heart mass increases as body mass does because of a greater workload, particularly in the presence of elevated blood pressure. A hypertrophic heart is common in obese persons and is a strong risk factor for HF. Concentric hypertrophy is more serious than eccentric hypertrophy in terms of

development of cardiac functional deficits. Understanding the mechanisms of obesity-related HF and implementing prevention and treatment measures could have a major impact on the prevalence and morbidity of this serious medical condition. Data are quite limited in scope; however, a number of weight loss studies, including studies of bariatric surgery patients, suggest that obesity-related cardiomegaly and impaired cardiac function often are reversible.

### Thrombogenesis and Procoagulant Risk

There are a paucity of data on the potential link between obesity and thrombogenesis and procoagulant risk. However, as noted in Figure 1, obesity is associated with increased prothrombotic and procoagulant states. Investigation of the relationship of plasminogen activator inhibitor-1 (PAI-1) levels to impaired fibrolytic functions in obesity and of the mechanisms by which obesity may induce thrombogenesis may yield important therapeutic information.

#### **Asthma**

The prevalence of asthma has increased concomitantly with the increase in obesity. Asthma could be caused by, and its symptoms aggravated by, an increase in BMI. The role of obesity-induced proinflammatory states or sympathetic nervous system changes are promising areas for asthma research; however, research in this area is very limited. Studies are needed to determine the mechanisms by which endocrine or inflammatory processes in obesity contribute to the onset or exacerbation of chronic inflammatory diseases such as asthma.

# Sleep Disorders

It is known that obesity can lead to obstructive sleep apnea (OSA), and there is some evidence that OSA may predispose individuals to weight gain and may further contribute to CVD. OSA triggers a range of neural, humoral, vascular, and inflammatory responses that warrant study. Compelling evidence exists that indicates that treatment of OSA by continuous positive airway pressure (CPAP) may decrease central obesity, lower leptin levels, and attenuate CVD conditions. Plasma leptin levels are markedly higher in obese men with sleep apnea than they are in obese men without apneic conditions, and research is needed to clarify the role of increased leptin levels in OSA and of OSA on subsequent comorbid disease development. In addition to evaluating OSA as an independent risk factor for obesity and vice versa, it is important to determine the contribution of OSA to metabolic syndrome.

# BASIC BIOLOGICAL ISSUES RELATED TO THE ETIOLOGY AND METABOLIC CONSEQUENCES OF OBESITY

Heredity is linked in fundamental ways to an individual's state of health and his or her risk for obesity and its health consequences. Basic research is needed to determine if the national epidemic of obesity is fueled by biological susceptibility. Research in the basic sciences that takes advantage of new technologies and emerging discoveries is imperative to further our understanding of the etiology and metabolic consequences of obesity and obesity-related diseases.

#### **Genetics**

Although the main causes of obesity are complex, multigenic, and environmentally mediated, an understanding of the contribution of genes that may predispose individuals to obesity is important and recent advances in genomics and proteomics offer key research opportunities. Research should continue on the identification of the multiple genes and allelic variants responsible for the predisposition to obesity and its comorbidities. Such studies are likely to be more successful if performed in the context of experiments designed to induce weight perturbations. Studies to identify genes will require large sample sizes, extensive phenotyping, longitudinal observations, and high-throughput DNA and gene-expression technologies. An important focus of genetic studies should be to identify gene-environment and gene-gene interactions. Ultimately, genetic evidence will contribute to the design and interpretation of epidemiologic and intervention studies. Although the effects of individual genes and proteins cannot be expected to explain a high proportion of body weight variation in the population, genomic and proteomic tools do offer possibilities for medical applications in obesity treatment, management, and prevention, including the development

of panels for identifying high-risk individuals early in life and/or selecting appropriate interventions and identification of new targets for drug treatments.

Research in these areas could benefit from increased interdisciplinary collaborations, the use of established biological samples, and the development of more powerful statistical approaches. For example, researchers can pool data to increase sample size, use phenotype data and DNA samples already available as well as initiate new collections to enhance existing data. Interdisciplinary and crossdisciplinary collaboration (e.g., studies involving geneticists, epidemiologists, and interventionists) is needed to advance the identification of successful interventions.

#### **Summary of Key Research Recommendations**

#### **Genetics**

- Identify and study genes and sequence variants responsible for:
  - The predisposition to gain weight and become obese
  - The fact that some obese persons develop associated morbidities while others do not.
- Define gene-environment and gene-gene interactions in the predisposition to obesity and its comorbidities, and investigate their potential contributions to the obesity epidemic and to the development of effective interventions.
- Identify the genes and mutations responsible for the most consistent quantitative trait loci from genomewide linkage scans for obesity.

# Adipose Tissue Biology and Biobehavioral Determinants of Food Intake, Fuel Regulation, and Fuel Partitioning

The discovery of the nutritional, genetic, and physiological interactions that govern human adipocyte metabolism is crucial to our understanding of the biological mechanisms and determinants of energy balance that link obesity to related chronic diseases. Remarkably few studies have evaluated the myriad important complex factors that affect adipose tissue secretion and their potential modifiers, which could hold the key to prevention and intervention strategies. For example, the regulation of adipocyte development, adipose tissue volume, and adipose tissue distribution is only partially understood. The developmental, endocrine, and nutritional triggers for preadipocyte proliferation and differentiation in different depots in animal models and humans are still to be elucidated. Research is needed to define the differences in adipose cells associated with distinct anatomical locations (such as visceral and subcutaneous abdominal sites). and the stimulatory factors that promote this process at various body sites and at various ages. The discovery of markers for preadipocytes or stem cells and the development of human adipocyte cell lines are essential if we are to identify the mechanisms involved in adipogenesis and fat remodeling. Adipose tissue is a secretory organ that releases a number of hormones and cytokines—including angiotensinogen, PAI-1, leptin, adiponectin, resistin, tumor necrosis factor alpha, interleukin-6—that are important because they have an impact on CVD, pulmonary, and other diseases. The relationship between these adipose tissue cytokines and systemic inflammation remains poorly understood. This area presents innumerable research opportunities.

Energy expenditure and its regulation are strong determinants of energy balance. Energy balance includes the energy expended in the basal state and at rest; the thermogenesis associated with the consumption, digestion, and storage of food nutrients; and the energy expended for activity. Although much has been learned over the last

decade concerning the regulation of food intake, little progress has been made concerning the regulation of metabolic rate and total energy expenditure. New cost-effective methodologies to measure metabolic rate and energy expenditure in free-living people and studies of the molecular mechanisms regulating metabolic rates under positive and negative energy balance conditions are needed.

Further research also is needed to elucidate the regulation of neurotransmitters and receptor systems in the central and peripheral nervous systems. Key areas needed include the identification of the critical afferent signals that control central nervous system pathways involved in energy homeostasis and the determination of which "downstream" hypothalamic neuronal systems participate in the control of energy homeostasis. A better understanding is needed of the autonomic nervous system and its role in weight regulation. Research is needed on the roles of sympathetic nervous system regulation of energy expenditure and partitioning; the long-term effects of caloric restriction on metabolic rates; and the association of DNA sequence variants at candidate genes to energy expenditure phenotypes in humans.

The different categories of appetite and satiety signaling within the brain need elucidation. An understanding of these kinds of modulatory influences on the overall regulation of body weight (e.g., how the efficacy of manipulations of the adiposity-signaling molecules leptin and insulin varies with genetics, diet, and gender) is an important priority.

### **Summary of Key Research Recommendations**

Adipose Tissue Biology and Biobehavioral Determinants of Food Intake, Food Regulation, and Fuel Partitioning

▶ Determine the mechanisms by which ectopic fat deposition occurs in skeletal muscle, liver, pancreas, heart, and other organs.

- Identify the pathophysiological mechanisms by which ectopic fat deposition increases:
  - The cluster of risk factors observed in the metabolic syndrome
  - The risks for CHD, stroke, hypertension, asthma, and sleep apnea.
- Investigate the mechanisms by which obesity entrains the metabolic syndrome, and the specific impact of excess abdominal, subcutaneous, and visceral adipose tissue.
- Identify mechanisms that regulate fuel mobilization and nutrient partitioning among tissues and organs in normal weight, obese, and formerly obese individuals under a variety of dietary practices.
- Determine how adipogenesis and adipose tissue expansion are regulated and why adiposity is defended under negative energy balance conditions.
- Identify molecular mechanisms regulating metabolic rates under positive and negative energy balance conditions.
- Determine the mechanisms by which key neuronal systems become resistant to hormones regulating food intake and energy balance, and the mechanisms by which calories and nutrient intake interacts with satiety signals.
- ▶ Elucidate the mechanisms by which obesity affects the inflammatory process, neuroimmunologic function, and sympathetic nervous system in cardiovascular and pulmonary disease.

# Critical Periods in Obesity Development

As obesity increases in prevalence and severity, it becomes more imperative to identify potential "critical periods" in an individual's lifetime that predispose to the development of obesity and that warrant targeted intervention strategies. A critical period is defined as a phase in life during which an individual may be at risk for an accelerated weight, waist, and/or adiposity gain. This higher risk may be caused by biological factors, behavioral factors, and/or by prior life events. Various periods throughout the lifespan are important to study in order to identify potential targets for effective interventions to prevent and treat obesity. They include fetal life, early infancy, early childhood, puberty, young adulthood, and for adult women, pregnancy and menopause.

Research on critical periods for weight gain would greatly benefit from the development of appropriate rodent and nonhuman primate models, from close interactions between basic science and clinical investigators, and from intervention designs that involve biologic, environmental, and behavioral components.

Multidisciplinary collaborative research is critical to determining whether presumed prenatal, early postnatal, childhood, puberty, and adulthood critical periods truly entrain subsequent weight and adiposity gains and by what mechanisms. In addition, the relationship of weight or adiposity gains experienced during these critical life periods to the development of obesity-related diseases must be studied.

#### **Summary of Key Research Recommendations**

# **Critical Periods in Obesity Development**

- Identify prenatal, early postnatal, childhood, pubertal, and adulthood events that entrain subsequent weight and adiposity gains and the related mechanisms, including hypotheses of critical periods for obesity development.
- Identify associations of weight or adiposity gains experienced at critical life periods with subsequent obesity-related cardiovascular and other diseases in cohorts followed over time.
- ▶ Determine the amount of physical activity necessary for the prevention of excessive weight gain during developmental periods and in adulthood.

### Diet and Physical Activity

The two most critical behaviors that determine weight gain are caloric intake and energy expenditure in all types of physical activity. The roles of diet and physical activity need to be understood in terms of their contributions to the biological processes that appear to be related to obesity. Although it is obvious that obese individuals consume more calories than they expend for prolonged periods of time, it is equally clear that the current obesity epidemic also is substantially driven by the progressive decline in energy expenditure related to work and leisure-time.

There are many research opportunities relevant to topics in the current public debate, including identification of optimal dietary macronutrient (fat, carbohydrate, and protein) content and evaluation of the impact of portion size, reducing energy density, calcium supplementation, fiber, and glycemic index for achieving and sustaining weight loss. Long-term diet studies are needed that use rigorous study designs.

Insufficient data are available to determine the specific roles of physical inactivity and activity in weight loss and prevention of weight gain and regain. A better understanding is needed of activity profiles that lead to the prevention of unhealthy weight gain, weight loss with optimization of body composition, and weight loss maintenance (including the role of activity intensity vs. the amount and the contribution of resistance exercise).

This area of research suffers from fundamental methodologic problems in measurement that must be resolved. Research is needed on the development of technologies to better quantify actual energy intake and measure physical activity in free-living people over extended periods of time.

#### **Summary of Key Research Recommendations**

### **Energy Balance: Role of Diet and Physical Activity**

- Determine the feasibility of achieving and sustaining small changes in energy intake, lifestyle, and physical activity and the impact of these changes on prevention of weight gain in the population.
- ▶ Develop strategies for helping people to control the portions of the foods and beverages they consume independently of the portion size presented.
- ▶ Conduct long-term studies to determine the effects of diets of different macronutrient composition on weight loss and adiposity, long-term maintenance of weight loss, and weight-related CVD risk factors.
- Determine the long-term consequences of high-fat, high-protein weight loss diets on lipid and lipoprotein metabolism, endothelial function, markers of coagulation and inflammation, glucose and insulin metabolism, blood pressure, and other cardiovascular risk factors.
- ▶ Determine whether any type of weight loss diet will produce a long-term weight reduction (e.g., weight maintenance for more than 5 years).
- ▶ Conduct long-term studies to determine the effects of new dietary manipulations on body weight and on glucose and lipid metabolism, such as calcium supplementation, increasing fiber intake, reducing energy density, and limiting foods with high glycemic index.
- Investigate the impact of regular physical activity on the metabolic syndrome and CVD manifestations at increasing levels of BMI and on the coupling between energy expenditure and caloric intake.
- ▶ Determine the combination of biological, behavioral, and environmental factors that predispose certain population subgroups (e.g., adults and children in several ethnic minority populations) to excess weight gain and difficulty in losing weight.
- ▶ Develop cost-effective, accurate methodologies to measure caloric intake and energy expenditure in free-living people.

# Developing Effective, Practical Prevention and Treatment Interventions Based on Better Understanding of Environmental and Societal Influences

The causes of obesity are embedded deeply within human biology and behavior, both of which are subject to a myriad of environmental and societal influences. Even without clarifying fully the biological determinants of development of obesity, it is certain that most, if not all, levels of susceptibility are enhanced by unfavorable environmental conditions—conditions that make overeating and inactivity possible and highly prevalent.

# Environmental and Societal Determinants of Food Intake and Physical Activity

Eating is one of the most deeply cultural and social acts in which humans engage and is essential for survival. Very little research has been conducted on environmental pathways influencing food intake at the population level, and even less is known about how existing food-related public policy helps or hurts the Nation's diet. Research to date has been largely descriptive, and systematic attempts to understand the nature and strength of specific environmental influences in relation to individual biological and behavioral regulatory systems are critically needed. Short-term studies are needed that examine relationships between environmental and social factors and hypothesized behavioral or biological intermediates related to obesity, and longer-term studies are needed that examine relationships between multiple hypothesized environmental determinants and obesity.

Numerous environmental factors can facilitate or limit physical activity. Societal-level determinants of physical activity are outside of the traditional health sector, and to study these determinants requires undertaking nontraditional (from a biomedical research perspective) approaches and partnerships. A forum should be established to foster interactions with and among key agencies and organizations in other sectors about physical activity

issues. Relevant agencies and organizations include those responsible for transportation, housing, land use, urban design, and occupational health and safety.

The opportunities for research are unprecedented, but the complexity of and interactions among the many obesity determinants present many challenges. There is an urgent need to clarify how environmental factors at different levels influence obesity development and how an environment more favorable to long-term regulation of weight within a healthy range can be established. Meeting this need will require conceptualization of how environmental and societal influences promote obesity. It will also necessitate the development of appropriate methods for monitoring these influences, incorporating them into interventions, and assessing relevant group and individual level outcomes.

Mechanisms are needed to ensure the timely evaluation of the effects of Federal, State, or local environmental and policy initiatives designed to reduce caloric intake or increase physical activity.

#### **Summary of Key Research Recommendations**

# **Environmental and Societal Influences on Food Intake and Physical Activity**

- Determine population secular trends in caloric and nutrient intake, energy expenditure of physical activity, and energy balance, including variations in important population subgroups defined by demographic characteristics.
- ▶ Elucidate the specific associations of acute and chronic poverty with obesity development and the related implications for other cardiovascular and pulmonary disease risks.
- ▶ Effects of recent changes in relevant government (Federal, State, and local) programs and policies on caloric intake and physical activity levels.

- Determine the influences of environmental and social factors on the obesity epidemic, including attention to social change and social process variables such as:
  - Technology that fosters inactivity
  - Marketing variables such as price, convenience, food portion size, and advertising and marketing of more and less healthful foods
  - Workforce dynamics
  - Poverty-related variables and policies regarding food and unsafe environments limiting physical activity
  - Consumers' ability to make informed food choices.
- Determine socially and culturally acceptable ways to minimize the effects on children in diverse ethnic and socioeconomic groups of societal-level environmental factors (particularly school and neighborhood characteristics) that predispose them to overeating and inactivity.
- Using community-based participatory research approaches, conduct large-scale "market research" studies in diverse communities of the acceptability of various environmental and societal changes that might be undertaken to promote healthier weight levels. Participation of community members in formulating and interpreting such research is desirable.
- Determine effectiveness of "media literacy training" to help raise awareness of potential adverse food marketing strategies in children and adults across diverse socioeconomic and cultural subgroups.

# The Family Environment

CVD and many other obesity-related chronic diseases run in families, as does obesity itself. Obese children are more likely to have obese parents and/or obese siblings. Research is needed on the ways in which familial eating and activity patterns are transmitted across generations.

The family and home are potentially very important environmental settings for both obesity development and weight control. Therefore, studies—both free-standing and embedded within intervention trials—are needed to identify modifiable family environment factors associated with obesogenic diets, physical activity, and sedentary behaviors for both adults and children. Family-based influences on obesity in adults have received little attention. Some potentially modifiable family environmental influences on childhood obesity have been identified in observational and laboratory-based research.

Family interventions focused on the child have been implemented in school settings and face-to-face with individual families or groups of families in their homes or communities, and without direct personal contact, have used mediated communications (e.g., phone, video, and written correspondence materials). Generally these interventions produce only modest short-term effects on diet and activity behaviors but not on anthropometric measures. The major barrier appears to be the difficulty of getting parents and other family members to participate in intervention studies. Evidence indicates that many families do not like the inherent intrusiveness of faceto-face or group interventions, and most parents prefer interventions that can be completed in their own home, particularly if these interventions involve their children. Prospective efficacy trials of family-oriented interventions, that overcome barriers and more effectively use clinical and public health settings and with long-term followup (more than 5 years), are needed.

Theory-based interventions are needed to improve the willingness/ability of family members to participate in obesity prevention and treatment interventions as well as to motivate and develop skills for all family members to encourage them to adopt more healthful behaviors. Research is also needed to determine if family-based treatments provide enhanced treatment efficacy to prevent, control, and treat obesity-related chronic diseases that run in families.

#### **Summary of Key Research Recommendations**

### **Family Environment**

- Use prospective observational studies to identify modifiable family environment factors associated with obesogenic behaviors, and the development of child and adolescent obesity.
- ▶ Conduct intervention research to determine ways to modify family environment factors associated with obesogenic diet, activity, and sedentary behaviors.

# Prevention, Treatment, and Applications to Clinical Practice and Community Settings

Obesity costs the United States more than \$117 billion each year, and its economic impact continues to escalate. Each year consumers spend more on programs and products designed to control body weight, and the market continues to expand. Meanwhile, the prevalence of overweight and obesity continues to increase unabated. It has been estimated that modifying energy balance by as little as 100 calories a day could prevent weight gain in most people. Prevention research is limited, and studies do not provide enough evidence to show that any one program can prevent obesity in adults.

The spectrum of obesity treatment research includes traditional calorie-reduction programs, with or without a physical activity component, that produce modest weight losses; more restrictive calorie-reduction approaches that result in greater weight loss; and other medical interventions such as pharmacological therapy and more invasive, bariatric surgery procedures. The treatment of obesity has improved over the past decade; however, long-term maintenance of weight loss remains a major problem. The development of effective methods for safe weight reduction and long-term maintenance of weight control is a major research priority. There is no "onesize-fits-all" diet and activity approach, and interventions used in research designs must meet the needs and interests of the individual as well as the population. Better pharmacological therapies also are needed, possibly including

plant-based therapies (e.g., complementary and alternative medicine). Focused research is needed to improve obesity-treatment outcomes in high-risk minority populations. Research to develop bariatric surgery procedures that are less invasive as well as studies of the long-term consequences of weight loss induced by these surgical procedures on hard endpoints, would be desirable.

Prevention research to identify factors predisposing to weight regain is a high priority, as is assessing whether such factors are the same in children and adults. Prevention, control, and treatment research should test the cultural appropriateness of key constructs and develop new approaches that include multiple institutions, sustain strong relationships with communities, and engage communities as partners. It is imperative that successful findings be translated and disseminated rapidly and monitored with improved surveillance systems. Randomized controlled trials are needed that move the science from efficacy to effectiveness. Effectiveness studies, implemented within health systems that first of all integrate obesity interventions with other health improvement and risk reduction strategies, but also integrate various settings in the context of the obesity interventions, i.e., clinical, worksite, patient-direct, and mass media, are needed to determine if this approach is strong enough to drive population-level impact. Such studies should focus especially on the outcomes of programs designed to "survive" in the marketplace.

#### Summary of Key Research Recommendations

# Prevention, Treatment, and Applications to Clinical Practice and Community Settings

- ▶ Define the natural history of obesity and determine the optimal periods for effective intervention.
- ▶ Develop and investigate the long-term effectiveness of novel approaches to increasing regular physical activity in adults.
- Identify and study phenotypes of overeating and other variables that have implications for the design of obesity treatment programs and that characterize degrees of responsiveness to treatment.

- ▶ Determine the effects on CVD, OSA, and other health outcomes of weight management interventions that:
  - Promote weight loss and prevent weight regain
  - Are designed for and delivered in primary care and public health settings
  - Include studies of alternative methods of delivering treatment including the Internet, telephone, and media outlets.
- Determine and study the relationships between BMI or adiposity phenotypes and cardiovascular and pulmonary disease risk factors and events among ethnic groups.
- ▶ Develop prevention and treatment interventions that:
  - Take advantage of special contexts (e.g., systems and organizations such as schools, worksites, community organizations, health maintenance organizations, public health clinic systems)
  - Evaluate the impact of environmental changes on both the system or organization and the attitudes and behaviors of the individuals within the system or organization
  - Include attention to compensatory or displacement effects occurring outside of the system or organization.
- ▶ Identify and characterize "best practices" related to obesity care.
- Identify how to use these best practices and other resources to develop, implement, and test office tools, procedures, protocols, and organizational systems in various primary care settings.
- Study extremes in the population in order to determine characteristics of persons resistant to obesity treatment in order to develop and target effective therapeutic approaches.
- Determine effective and practical ways to prevent the progression to complications—especially CVD and related comorbidities—in adults with established obesity, especially individuals with metabolic syndrome.

### Research Training and Mechanisms

Research training and mechanisms were not topics scheduled for discussion at the Think Tank meeting. However, they repeatedly came up in discussion, and specific recommendations made by the participants are noted below.

#### Summary of Key Research Recommendations

### **Research Training and Mechanisms**

- Establish interdisciplinary training grants at the masters, doctoral, and postdoctoral levels of study to specifically foster and support the development of research scientists focused on:
  - Determining the causes of obesity
  - Increasing the public health relevance of obesity research
  - Enhancing interventions that target obesity prevention.
- Using a model similar to the NHLBI Nutrition Academic Awards, establish a program of obesity academic awards for undergraduate and graduate medical education and continuing medical education.
- Support obesity intervention training for primary care physicians.
- Support short- and long-term crosstraining programs that combine laboratory and field methods for population-based nutrition and physical activity research.
- Using a model similar to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) obesity research centers, establish additional evidence-based centers that can serve as training and research centers for both new and established investigations.

# Some Consumer and Professional Society Perspectives

The perspectives of representatives of the various consumer and professional organization constituencies provided critical input into the Think Tank dialogue. Their perspectives were complementary to those of the other session presenters, and many of their research recommendations are reflected in the key research recommendations described above. For example, the urgent need for tools applicable to primary care and for involvement of community practice networks was stressed by the American Academy of Family Physicians. The American Heart Association underscored that its obesity research activities and conferences complement those of the Federal Government. The number of bariatric surgeries performed in the United States is increasing rapidly (at a cost of \$2.8 billion last year), and a representative of the American Society for Bariatric Surgery discussed the possible side effects and raised possible important research issues, such as why conditions such as Type 2 diabetes and asthma are ameliorated in some patients who have had the surgery. The need to counteract discrimination against obese people in clinical settings (e.g., causing people to avoid or delay screening and treatment) was emphasized as a health care access problem by the Council on Size and Weight Discrimination. Additional clinical issues relevant to obesity—such as reimbursement, training for health care professionals, fraudulent treatment, and recognition of obesity as a chronic disease that causes other diseases—were emphasized by the North American Association for the Study of Obesity. The obesity epidemic also is reflected in the military population, and the unique clinical research opportunities with the more than 9 million potential subjects available for longitudinal study were discussed by a representative of the Cardiac Risk Prevention Center at Walter Reed Army Medical Center.

# Setting a Research Agenda To Help Americans Achieve and Maintain a Healthy Weight

The Nation's "obesogenic environment" appears to have different potency in different groups. An understanding of these group differences could lead to the development of effective public health solutions. Broad-based research on obesity prevention and treatment requires action on several fronts—basic and practical applications—in order to have an immediate public health impact. Concurrent research on accelerating and enhancing the evolution of long-term solutions to the combined problems of obesity and its associated health outcomes should be conducted.

To embrace fully the public health research questions will require reframing the concept of obesity research to go beyond the traditional biomedical paradigms and research designs to:

- Incorporate, aggressively, theoretical models and methods from the social and policy sciences.
- Collaborate with scientists and professionals who understand the content and process of systems in which societal causes of obesity may be rooted or potential solutions may be found (e.g., marketing, urban planning, food science, transportation, and media).
- Conduct multilevel studies in which the interplay of more and less proximal forces that influence energy balance and body weight can be assessed simultaneously.
- Establish a forum to foster interactions with and among key agencies and organizations in other sectors about energy balance issues.

There are major research gaps with respect to all aspects of energy balance and specific mechanisms whereby adiposity results in negative consequences on various target tissues. Similarly, there is an urgent need for studies of population-level interventions to decrease environmental factors that encourage obesity. Such studies may be most informative if they include individualized assessments of both biological and behavioral factors that may predispose the individual to weight gain and obesity. Because families share genes, behaviors, and environments, family-based studies may offer particular advantages in this respect.

The diversity and number of research recommendations reflects the dilemma associated with the need to cover all of the bases. The recommendations reflect uncertainties about the utility of currently available strategies for obesity prevention and treatment. The recommendations also reflect an appreciation for the continuing need for basic research. Trade-offs between using resources to act on the things that we can do right away versus conducting research to obtain new insights about possible solutions, will need careful consideration.

The overall direction of the next generation of obesity research is to continue building the evidence base in order to determine the most effective, efficacious health promotion strategies and treatments, especially in high-risk populations. To the extent that we already have substantial evidence regarding environmental and behavioral determinants of obesity as well as the beneficial effects of certain types of interventions on CVD outcomes, there is a pressing need for research to refine our understanding of the practical relevance of these findings for the general population to ameliorate the problems of overweight and obesity in the substantial numbers of U.S. adults and children who are affected. To accelerate progress, it is imperative that research be informed by an overarching vision and with a broad perspective of what knowledge is needed in order to curb this epidemic.

The next generation of research, focusing specifically on obesity treatment, must be more translatable in order to reach diverse populations in community settings as well as in routine clinical practice. Systematic observations in population-based natural or "real world" settings can clarify links between specific environmental characteristics and specific eating or activity behaviors that predispose individuals to obesity and provide viable hypotheses about where and how to intervene to prevent obesity and promote weight control and weight loss and maintenance.

No single individual or group can meet these challenges alone. The full report summarizes in greater detail the deliberations and recommendations from the Think Tank, which have implications not only for NHLBI-sponsored research but also for obesity research overall. This national and global public health challenge—and the responsibility—must be collaborative in nature.

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