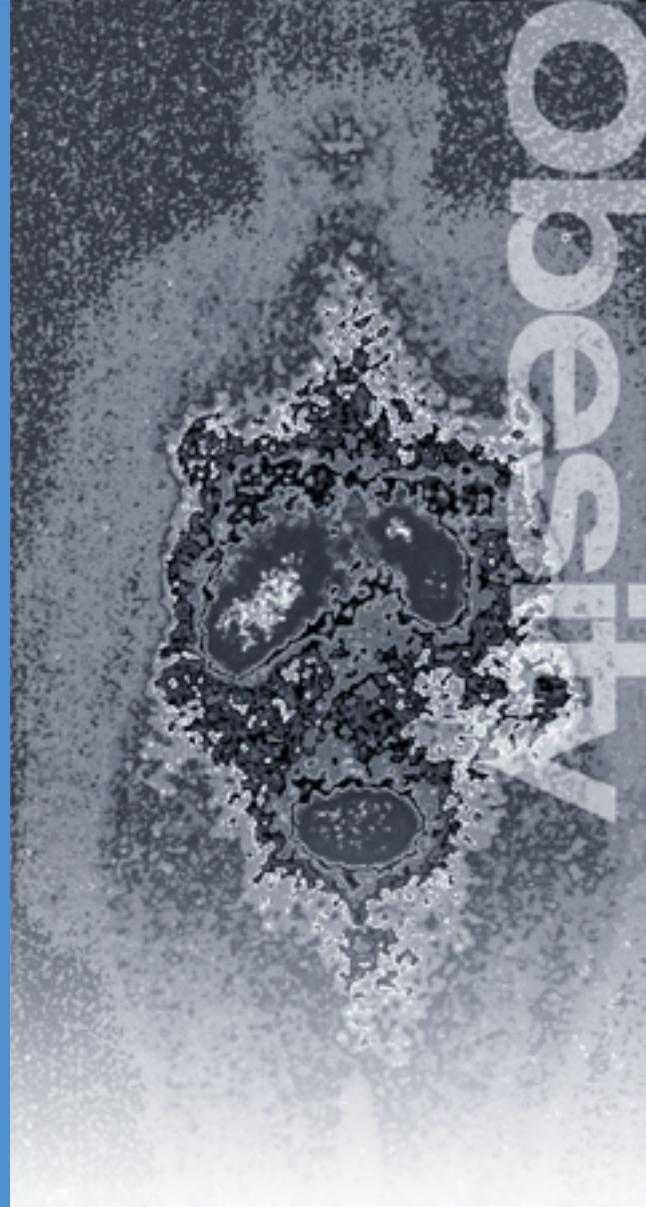


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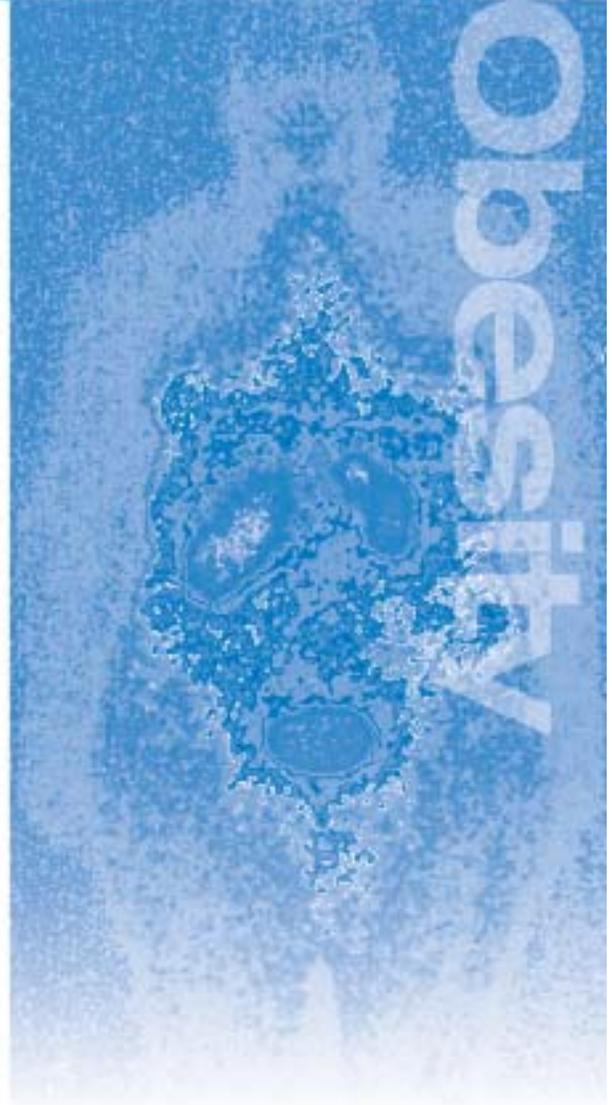
# Enhancing Obesity Research at the National Heart, Lung, and Blood Institute



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



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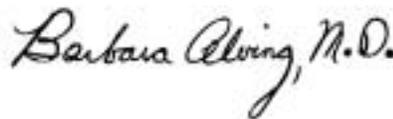
As a Nation, we are confronted with an unprecedented obesity epidemic—the solution to which will be as complex in its nature as the epidemic itself. An obesity epidemic, as well as the dramatic parallel increase in associated comorbidities such as heart disease, diabetes, and asthma can be considered 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.



Barbara Alving, M.D.

Acting Director  
National Heart, Lung, and Blood Institute  
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National Institutes of Health



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## Background

### 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 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.

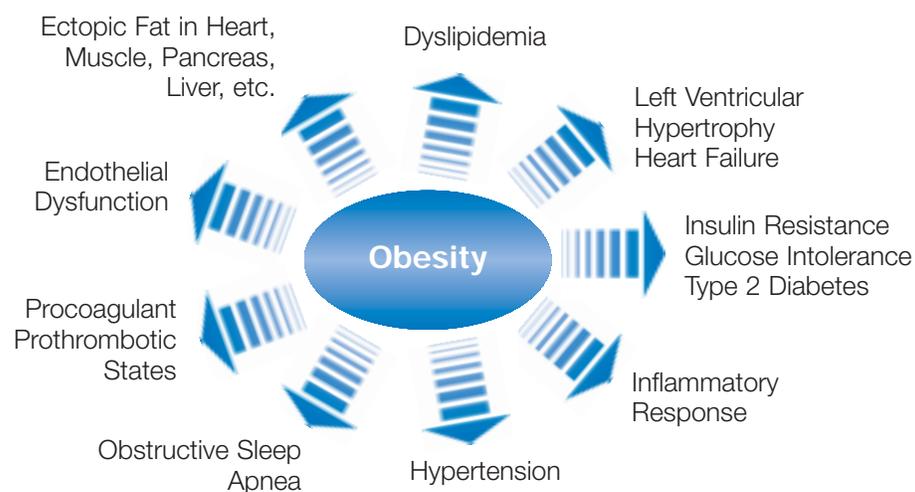
CVD imposes a large morbidity, mortality, and economic burden on individuals, families, and the Nation. Common forms are atherosclerosis, hypertension, chronic obstructive pulmonary disease, and blood-clotting disorders. The most serious atherosclerotic diseases are coronary heart disease (CHD), as manifested 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

FIGURE 1  
**Obesity and Cardiovascular Risk**



Modified from Sharma 2002. Source: Reprinted by permission from Nature Publishing Group (Sharma, AM. Adipose tissue: a mediator of cardiovascular risk. *International Journal of Obesity and Related Metabolic Disorders* 2002;26, Figure 3, page S6) copyright 2002 Nature Publishing Group.

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 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 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

TABLE 1

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

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

\*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.

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.

# Research Recommendations

## 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

### 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 and study the genes and mutations responsible for the most consistent quantitative trait loci from genome-wide linkage scans for obesity.

crossdisciplinary collaboration (e.g., studies involving geneticists, epidemiologists, and interventionists) is needed to advance the identification of successful interventions.

### **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 cardiovascular, 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, Fuel 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 versus 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 face-to-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 “one-size-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
  - Design for and deliver 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 lung 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 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.

## Conclusion

### 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

**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.

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.

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 report sections that follow summarize 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.**



## Obesity—The Unchecked Epidemic

The impetus for the effort by the NIH's NHLBI to identify new research directions and opportunities to help prevent and treat overweight and obesity originated with a number of important Federal sources. Overweight and obesity are among the most important Leading Health Indicators in *Healthy People 2010*, the Nation's health objectives for the first decade of the 21st century (DHHS, 2000). The *Surgeon General's Call to Action To Prevent and Decrease Overweight and Obesity 2001* not only identified overweight and obesity as a national epidemic but designated it the most important public health challenge of our time (DHHS, 2001). On June 20, 2002 the President launched *HealthierUS*, a disease prevention and health promotion initiative to improve the health of Americans through modest changes and improvements in their daily activities, including good nutrition, regular physical activity, and common sense behavior that will prevent disease and improve health. Concurrently, the DHHS Secretary has identified obesity as a central priority and is leading a new department wide effort—*Steps to a HealthierUS*—which targets the prevention of diabetes, asthma, and obesity at the community level (DHHS, 2003). More recently, NIH has undertaken a series of specific activities to see how the Institutes can address issues relevant to the obesity epidemic.

NHLBI recognizes that the epidemic of obesity is a problem at the forefront of American public health concerns and considered it imperative to convene experts in a wide range of fields so that they could provide their collective thoughts and recommendations to the Institute. Thus, the Institute convened a 2-day *Think Tank on Enhancing*

*Obesity Research at the NHLBI* on March 24–25, 2003, in Bethesda, MD. The experts who were gathered for the Think Tank are prominent in obesity research and research application, and the results of their deliberations provide invaluable information and tools that will contribute to our greater effort to tackle the obesity problem.

### Organization of This Report

This report was produced through the collaborative work of the participants. The initial manuscript was prepared by the cochairs with contributions from the Think Tank presenters. The entire report was reviewed by the NHLBI and NIH participants.

The Executive Summary of the report outlines the recommended priorities for enhancing the NHLBI obesity research efforts in areas considered to be the most promising for future research.

The genesis for the Think Tank, the organization of the report, the magnitude of the problem, and the relationship of obesity to diseases under the purview of the NHLBI are described briefly in this section. Research recommendations make up the bulk of this report and describe—in three parts—the numerous current and future opportunities for enhancing obesity research. Highlighted first are the biological issues related to the etiology of obesity and to the metabolic consequences of obesity, including genetics, adipose tissue biology, nutrient partitioning, regulation of food intake, fuel regulation, critical periods, and diet and physical activity. The second part focuses on the environmental and societal influences including the

family environment, on food intake and physical activity, and on prevention and treatment models and their applications to clinical practice and community settings. The final part summarizes the perspectives of representatives from various consumer and professional constituencies who provided critical input into the Think Tank recommendations.

The report conclusion presents critical research needs that were identified by the Think Tank participants and summarizes the research implications. In contrast to the Executive Summary, this section groups the same recommendations according to research categories identified as part of the NHLBI research spectrum. Although there is often overlap in the research approaches that can be used to address these research questions, each was assigned to the category related to the most immediate need. The implications of these recommendations are summarized for the next phase of obesity-related research.

The list of references contains those that the participants cited in the report. The report concludes with three appendices: the list of contributors to this report and Think Tank participants; agenda for the Think Tank on Enhancing Obesity Research at the NHLBI; and a list of acronyms and abbreviations.

## Magnitude of the Problem

Calling obesity in the United States an epidemic or pandemic is more than rhetorical. The increased prevalence illustrates alarming trends for people of all ages, racial/ethnic groups, and genders. The prevalence of obesity is increasing in almost every population that has been studied (WHO, 2000; Ebbeling et al., 2002). The ecological explanation centers around the observed changes in dietary and physical activity behaviors that have occurred at a pace unprecedented in history and not only in developed countries, but also in countries in economic transition (Drewnowski and Popkin, 1997).

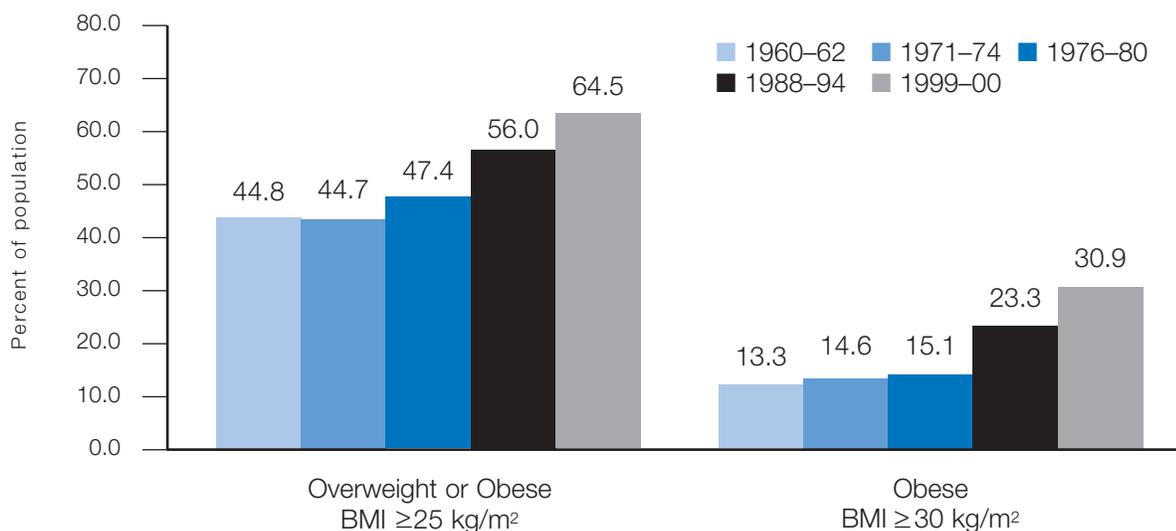
Obesity is assessed using the BMI measure: weight (kg) divided by height (m) squared.

From a practical perspective, BMI can be estimated readily and reliably from height and weight measurements in both clinical and community settings. Although an indirect and incomplete measure of fatness and body fat distribution, BMI is strongly correlated with percentage of body fat and is closely associated, both epidemiologically and clinically, with the occurrence of diabetes, cardiovascular and pulmonary diseases, musculoskeletal disorders, and some cancers (NHLBI, 1998; WHO, 2000). As defined by the accepted criteria of a body mass index (BMI) of 25–29 kg/m<sup>2</sup> for overweight and a BMI of 30 and over for obesity, the latest (1999–2000) National Health and Nutrition Examination Survey (NHANES) data indicate that 65 percent—approximately 122.5 million—of American adults are overweight or obese and 31 percent are obese (Flegal et al., 2002). Using the current growth reference for children, NHANES data indicate that more than 15 percent—approximately 9 million—of children and adolescents are overweight (Ogden et al., 2002). These striking trends are illustrated in figures 2 and 3.

Within the United States, differences in the prevalence of obesity by geographic area (i.e., State) and by race/ethnicity have been noted for many years. Of particular concern are African American women, who have had higher rates of obesity than white women for decades and whose CVD risk factor profiles are characterized by notably higher-than-average mortality from heart disease, stroke, and diabetes (DHHS, 2003). This gap continues to widen. In the 1999–2000 National Health and Nutrition Examination Survey, the prevalence of obesity (BMI of 30 kg/m<sup>2</sup> or above) was 50 percent among African American women, 28 percent in African American men, 30 percent in nonHispanic white women, and 27 percent in nonHispanic white men (Flegal et al., 2002). Fifteen percent of African American women are identified as being class-3 obese (BMI of 40 kg/m<sup>2</sup> or more, equivalent to about 100 pounds or more overweight). Excess obesity in African American females is now a problem even during childhood and

FIGURE 2

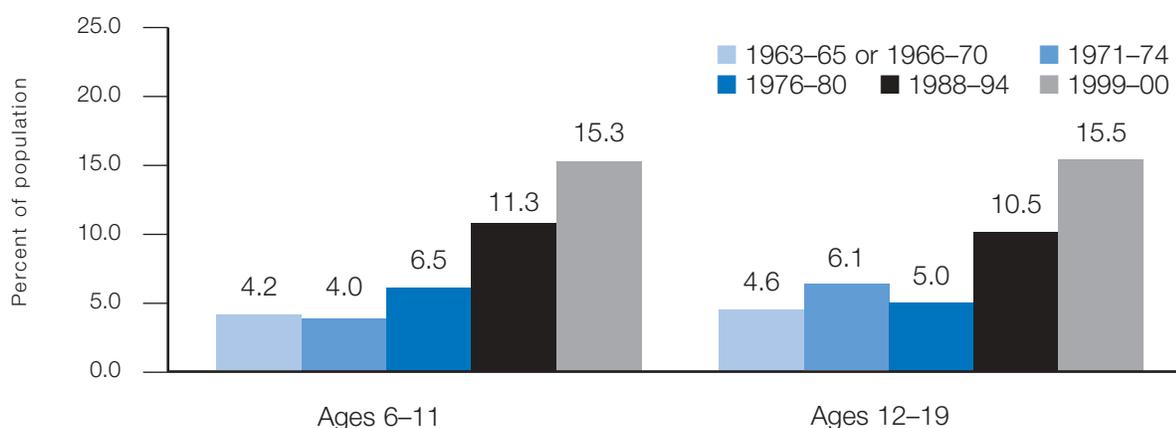
**Overweight and Obesity in U.S. Adults (Both Sexes Combined) Ages 20–74, Age Adjusted.**



Source: *Health, United States*, Table 70, CDC, 2002.

FIGURE 3

**Overweight Children and Adolescents in the United States (Both Sexes Combined).**



Source: *Health, United States*, Table 71, CDC, 2002. Note: Overweight is defined as at or above the sex- and age-specific 95th percentile BMI cutoff points from the 2000 CDC Growth Charts. Data for 1963–1965 are for 6–11-year-olds and for 1966–1970 are for 12–17-year-olds (not 12–19-year-olds).

adolescence (Ogden et al., 2002). Obesity prevalence also is disproportionately high in Mexican American women (Flegal et al., 2002), other Hispanic populations, and American Indians and Pacific Islanders (NHLBI, 1998).

Factors that may contribute to higher rates of obesity in African American women

include genetic or intrauterine environmental influences on the regulation of energy intake or expenditure; maturational and reproductive factors; attitudinal, behavioral, and underlying cultural determinants of energy intake or expenditure and weight management; and other determinants of long-term weight regulation, including effectiveness of voluntary weight control (Kumanyika, 1987).

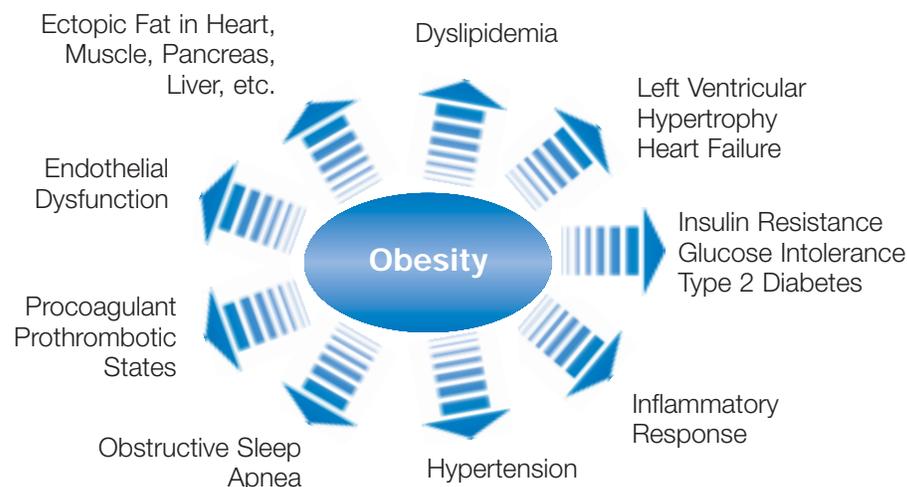
The accelerated trend of obesity in African American girls is a new component of the overall burden of obesity in African American females. The NHLBI Growth and Health Study suggests several environmental and behavioral influences on both food intake and physical activity that may contribute to this problem (McNutt et al., 1997; Kimm et al., 2001; Kimm et al., 2002).

Evidence is accumulating that increased rates of diabetes, heart disease, and other obesity-associated morbidities are following on the heels of increases in body weight around the world (WHO, 2000). This growing epidemic of obesity is of particular relevance to NHLBI because of the clearly documented associations of obesity with a number of cardiovascular and lung disease risk factors and outcomes, including CVD mortality, abnormal CVD risk-factor profile, the presence of several features of metabolic syndrome, obstructive sleep apnea, and asthma (as listed below and illustrated in figure 1). A conver-

gence of data indicate that obesity is associated with a higher prevalence of or risk for:

- Coronary artery disease
- Heart failure
- Cardiovascular mortality
- Stroke
- Hypertension
- Dyslipidemia characterized by high triglycerides, low HDL cholesterol, and high apolipoprotein B, or a profile of small, dense LDL-cholesterol particles
- Metabolic syndrome
- Sleep apnea
- Asthma
- Type 2 diabetes mellitus, in both adults and children
- Disability
- Endothelial dysfunction
- Procoagulant and prothrombotic states
- Inflammatory markers
- Insulin resistance and glucose intolerance
- Albuminuria
- Renal hyperfiltration

FIGURE 1  
**Obesity and Cardiovascular Risk**



Modified from Sharma 2002. Source: Reprinted by permission from Nature Publishing Group (Sharma, AM. Adipose tissue: a mediator of cardiovascular risk. *International Journal of Obesity and Related Metabolic Disorders* 2002;26, Figure 3, page S6) copyright 2002 Nature Publishing Group.

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

## Cardiovascular Disease

Morbidity and mortality rates from CHD, stroke, heart failure, cardiomyopathy, and possibly arrhythmia/sudden death are associated with overweight, obesity, and abdominal fat (Eckel et al., 2002; NHLBI, 1998). In the Framingham Heart Study, an increase in the risk ratio for coronary events was observed in individuals with a BMI greater than 30, as well as an increase in age-adjusted relative risk associated with an increased number of risk factors in the overweight group (i.e., those with a BMI between 25 and 30) (Kannel, 2002). Observational studies have shown that overweight, obesity, and excess abdominal fat are related directly to CVD risk factors, including high levels of total cholesterol, LDL cholesterol, triglycerides, blood pressure, fibrinogen, and insulin (Haffner et al., 1991), and low levels of HDL cholesterol (NIH, 1985). The relationship between adipose tissue excess, abdominal fat distribution, and CVD in part may reflect the higher turnover of adipose tissue-free fatty acids that often results in insulin resistance but other mechanisms are also thought to be involved.

Adipose tissue also secretes hormones and cytokines that potentially are atherogenic and pro-inflammatory. (See the discussion of adipose tissue biology). For example, leptin, adiponectin, and resistin are synthesized by adipocytes and they have complex and incompletely understood roles at distant sites. Although leptin inhibits energy intake and promotes energy expenditure, leptin resistance typically accompanies obesity. Evidence suggests that leptin may be pro-atherogenic, and it has been associated with carotid thickening, hemorrhagic cerebral vascular accident, and oxidative damage to endothelial cells. Adiponectin promotes insulin action in muscle and has other properties suggesting that it is anti-atherogenic.

Finally, adipose tissue produces cytokines—e.g., tumor necrosis factor- $\alpha$  and interleukin-6—that stimulate C-reactive protein (CRP) production by the liver. Elevations of CRP are common in obesity and may relate to increased risk of CVD. Increase in visceral adipose tissue and waist girth each are associated with increases in CRP levels (Lemieux et al., 2001). The ectopic deposition of lipid in heart muscle and other organs that accompanies obesity also is of concern. This phenomenon of abnormal lipid deposition in skeletal muscle and organs has been referred to as “lipotoxicity” (Unger et al., 1999).

A better understanding is needed of the mechanisms by which low HDL-cholesterol levels develop with increasing adiposity and how low HDL relates to the augmented cardiovascular morbidity and mortality rates in the obese. The pathophysiology—especially the functional and metabolic consequences of fat deposition in nonadipose tissues and organs and the risk for CVD—must be investigated. Investigation of the pathophysiological mechanisms by which the predominance of abdominal adipose tissue leads to CVD and how this tissue volume is regulated warrants further investigation. Researchers must identify the mechanisms and understand why the human body defends its adipose tissue mass. Finally, the relationship between endothelial dysfunction, inflammation, and CVD requires further study, especially to identify what regulates the production and secretion of hormones and cytokines from adipose tissue.

## Hypertension and Hemodynamic Disturbances

Data from NHANES III show that the age-adjusted prevalence of high blood pressure increases progressively with higher levels of BMI in men (from approximately 18 percent at a BMI <25 to 38 percent at a BMI  $\geq$ 30) and in women (from approximately 16 percent at a BMI <25 to 32 percent at a BMI  $\geq$ 30) (Brown et al., 2000). The direct and independent association between blood pressure and BMI or weight has been shown in numerous cross-sectional and prospective

studies (JNC 7, 2003; NHLBI, 1998). The pathophysiology underlying the development of hypertension associated with obesity involves sodium retention and associated increases in vascular resistance, blood volume, and cardiac output. However, the precise mechanisms are poorly understood.

Adipose tissue releases angiotensinogen. Angiotensinogen converts renin to angiotensin I, a precursor to the vasoactive peptide angiotensin II. The importance of the renin/angiotensin system (RAS) to the hypertension of obesity, however, is not clear (Mertens and Van Gaal, 2002). Scientists must determine why some obese people become hypertensive while others do not. Studies to better understand the mechanisms underlying the relationship between obesity and development of hypertension are also needed.

The mechanisms that link obesity to hemodynamic disturbances and impaired kidney function also are poorly understood. Obesity leads to diabetes, which is a major cause of end-stage renal disease (Hall, 2003). How obesity contributes to the development of abnormal glomerular function and eventually kidney failure warrants further investigation.

### Metabolic Syndrome and Its Constellation of Risk Factors

Obesity is associated with metabolic syndrome, a condition described by the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III or ATP III) (NCEP, 2002). Although it continues to emphasize that elevated LDL cholesterol is a major cause of CHD, ATP III also calls attention to primary prevention in individuals with multiple lipid and nonlipid risk factors of metabolic origin. The metabolic syndrome represents a constellation of cardiovascular risk factors that occur in one individual. The diagnosis is based on five factors and the metabolic syndrome condition is said to be present when three or more

of the risk factors are present (see table 1). It has been noted that some males may develop multiple metabolic risk factors when the waist circumference is only marginally increased, e.g., 94–102 cm (37–40 in). These males may have a strong genetic contribution to insulin resistance and should also benefit from life style changes (NCEP, 2001).

TABLE 1

#### 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

\*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.

Researchers have determined that the age-adjusted prevalence of the metabolic syndrome, as defined in ATP III, is approximately 24 percent among American adults 20 years and older (Ford and Giles, 2003). Persons with the metabolic syndrome are at increased risk of developing CVD. Because most people with the metabolic syndrome also are insulin resistant, they have an increased risk for developing of type 2 diabetes. Although obesity is thought to be an underlying cause of metabolic syndrome, adipose tissue hormones and cytokines, ectopic lipid infiltration and abnormal fat distribution (e.g., predominant abdominal obesity) even in the presence of a normal body weight could all be involved. Many investigators believe that persons with a

genetic propensity to insulin resistance are most likely to develop the metabolic syndrome when they gain weight. Increasingly, evidence indicates that genetic susceptibility for each of the risk factors of the metabolic syndrome can worsen its clinical expression.

Research is needed on the role played by a sedentary lifestyle in the cause or development of the metabolic syndrome and on differences between men and women in different ethnic groups at various phases of life. Whether a premetabolic syndrome condition can occur in children or in young adults should be investigated. The definition of the metabolic syndrome may be broadened to include other risk factors, such as proinflammatory and prothrombotic states. This area needs further evaluation. Finally, a better understanding of the true predictive value of the metabolic syndrome for future cardiovascular events is necessary.

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

Excess adiposity, directly or indirectly, has been documented as an important and independent risk factor for heart failure (HF) in a number of studies, including in the Framingham Heart Study (Hubert et al., 1983). HF is a frequent complication of severe obesity and a major cause of death among the obese; the length of time an individual has been obese is a strong predictor of HF (Shimizu and Isogai, 1993). Mortality rates from HF increase as a function of increased BMI (Kenchiah et al., 2002). Heart mass increases with growing body mass as a result of a greater workload, particularly in the presence of elevated blood pressure (Heymsfield et al., 1992; Messerli et al., 1983). The hypertrophic heart that often is observed in obese individuals is a strong risk factor for congestive HF (Kenchiah et al., 2002). Concentric hypertrophy is more severe than eccentric hypertrophy in terms of development of cardiac functional deficits (Contaldo et al., 2002; Heymsfield et al., 1992; Messerli et al., 1983; Messerli et al., 1987). A number of weight-loss studies, including those involving bariatric surgery

patients, suggest that obesity-related cardiomegaly and impaired function often are reversible (Heymsfield et al., 1992; Hinderliter et al., 2002).

Current data are limited in scope, and further research is needed on the relationship between weight and the risk of heart failure in obese individuals among different ethnic groups and in diabetic subjects. In addition, the relationship between obesity and the concentric and eccentric forms of heart hypertrophy needs more evaluation.

### **Thrombogenesis and Procoagulant Risk**

Prothrombotic states have been observed in obese individuals as well as in individuals with the metabolic syndrome (Giovanni et al., 2002). However, few data are available to help us understand this important relationship. Adipocyte and stromal vascular cells are known to secrete plasminogen activator inhibitor-1 (PAI-1), which may be implicated in the development of the prothrombotic state observed in obese persons. Increases in PAI-1 also may be secondary to the insulin resistance so commonly found in obesity. Insulin inhibition of platelet/collagen interaction appears to be absent in obesity—this, combined with the inflammation common to obesity, is thought to increase platelet aggregation. Evidence is accumulating that changes in the coagulation system (fibrinogen, FVII, FVIII, vWF) and the fibrinolytic system (PAI-1, tPA) are associated with various degrees of obesity, body fat distribution, and insulin resistance (Mertens and Van Gaal, 2002; McGill, 1994). Obesity also is associated with higher rates of pulmonary thromboembolic disease (Goldhaber et al., 1997). Leptin also may play a role in increased platelet aggregation and arterial thrombosis (Konstantinides et al., 2001).

The obesity-related factors that increase the prothrombotic state such as PAI-1 and fibrinogen and that may be related to morbidity from CVD require further study. Determination of the underlying mechanisms, whether

the outcome measures represent cause or effect, and the effect of weight loss on these systems is critical to furthering our understanding of these important issues.

## **Asthma**

Asthma has doubled during the past two decades and its prevalence parallels that of the advancing obesity epidemic—the aggregation of these two together is disturbing. The prevalence of obesity is extremely high in children in the inner city, who are at the greatest risk of developing asthma (Luder, 1998). The relationship between asthma and obesity is an understudied area and represents an important research opportunity to elucidate the suggested link between the concurrent rises in these two widespread public health problems.

Increased BMI is associated with the development of asthma (independent of other risk factors) in adults and children. For example, girls who become overweight between the ages of 6–11 have a seven times greater risk of developing asthma at age 11 or 13 than girls who do not (Castro-Rodriguez et al., 2001). Also, the Nurses Health Study, after controlling for a number of potential covariates (including physical activity) found that women who had a significant weight gain after age 18 have an increasing—up to 2.7—relative risk of developing asthma (Camargo et al., 1999). The relative risk of incident asthma in obese individuals (BMI >30) was three times that of lean individuals (BMI <20) (Camargo et al., 1999). Data from CARDIA, controlling for physical activity, looked at disease incidence and prevalence during the decade of followup. Progressive asthma incidence was observed in young adults, with the greater effect in women (Beckett et al., 2001).

Further, being overweight has been associated with lower lung function, increased daily asthma symptoms, and more frequent exacerbations. Girls who were obese at the time of puberty were found to experience wheezing or

a new onset of wheezing at puberty which is associated with the establishment of lifelong wheezing (Castro-Rodriguez et al., 2001). Clinical trials have indicated that weight loss improves asthma, breathing, and other clinical outcomes and has decreased medication use by those who have lost weight.

Obesity and asthma are both proinflammatory states. Asthma is an immunologic disease and its relationship to leptin and other obesity-related hormones is also important to study. Obesity and asthma also share a number of linked regions and candidate genes; thus a better knowledge of the interaction between genes and the environment will benefit both. A recent NHLBI workshop on asthma and obesity identified many research opportunities in the field, some of which are summarized below.

The interactions between genetic factors, obesity, and asthma need to be investigated. The effects on the immune system and inflammatory pathways associated with the proinflammatory states often observed in obese individuals and in those who have asthma should be studied. Similar mechanisms may be important in both conditions. Even though the relationship between the sympathetic nervous system and obesity has been explored by various studies, the associations with asthmatic conditions should be investigated further. Finally, the pathobiological links between obesity and asthma must be explored in order to identify potential intervention targets that may lead to the prevention of asthma (Weiss and Shore, 2004).

## **Sleep Disorders**

Obstructive sleep apnea (OSA) occurs when an individual's airflow stops intermittently during sleep because of upper airway collapse during inspiration. Despite strenuous efforts to breathe, apnea may persist for more than 30–45 seconds with consequent CO<sub>2</sub> retention and oxygen desaturation to levels as low as 30–40 percent. These apneic

events trigger a range of neural, humoral, vascular, and inflammatory responses. Increasing evidence shows that OSA is linked to acute and chronic CVD.

Approximately 25 percent of middle-aged and older men and 10 percent of middle-aged and older women have significant OSA. Obesity, particularly upper-body obesity, is the most powerful risk factor for the development of sleep apnea. Approximately 40 percent of morbidly obese individuals have clinically significant sleep apnea (Vgontzas et al., 1994). A 1 percent decrease in body weight may result in a 3 percent decrease in the severity of sleep apnea.

Although obesity clearly is a risk factor for OSA, some research indicates that sleep apnea may predispose individuals to weight gain (Phillips et al., 1999). Plasma leptin levels are markedly higher in obese men with sleep apnea than in those without apneic conditions, suggesting that the “leptin resistance” that may be associated with obesity is even more marked in patients with OSA (Phillips et al., 2000). Daytime fatigue and somnolence, together with carbohydrate hunger evoked by sleep deprivation, also may contribute to weight gain in OSA.

There is compelling evidence that treatment of OSA by continuous positive airway pressure (CPAP) results in a decrease in visceral fat, no change in subcutaneous fat, or lower leptin levels (Chin et al., 1999). The dyad of obesity and sleep apnea may increase the risk of hypertension, atrial fibrillation, and heart failure (Malone et al., 1991; Peppard et al., 2000). Treatment of OSA can lower blood pressure in hypertensive patients, improve cardiac function and exercise tolerance in HF patients, and perhaps decrease the likelihood for recurrence of atrial fibrillation.

Studies on the causes of OSA and the triggering mechanisms brought about by obesity are needed. Conversely, the role of OSA in development of obesity, especially childhood obesity is important. The contribution of

bariatric surgery to alleviating the symptoms of sleep apnea and the mechanisms involved also should be evaluated thoroughly. Finally further study is warranted on the role of leptin and other metabolic changes observed in OSA.



## Basic Biological Issues Related to the Etiology and Metabolic Consequences of Obesity

### Genetics

Studies on the familial risk for obesity have shown that the relative risk for a first-degree relative of a proband with a weight problem is only about 2 if the proband has a BMI 25–30, but reaches as high as 3 for a BMI of 30, 4 to 5 for a BMI of 35, and 6 to 7 for BMIs greater than 40 (Lee et al., 1997). However, it is clear that the familial risk is not entirely due to genetic factors, as the spouse of a proband with obesity also has an increased risk of obesity, although to a lesser degree (Katzmarzyk et al., 1999).

A fundamental question is whether the current epidemic is fueled by a growing prevalence of biological defects that would put an increasing number of people in positive energy balance for long periods of time. Three lines of evidence support this hypothesis. First, 33 Mendelian disorders (at last count) exhibit excess weight or frank obesity as one of their manifestations. All of them have been mapped to a chromosomal region of the human genome and for some of them the defective gene has been identified (Chagnon et al., 2003). Second, specific mutations in six genes—leptin gene (LEP), leptin receptor gene (LEPR), melanocortin-4 receptor (MC4R), proprotein convertase subtilisin/kexin type 1 (PCSK1), proopiomelanocortin (POMC), and single-minded (*Drosophila*) homolog 1 (SIM1)—have been shown to cause obesity (Chagnon et al., 2003). These are known as nonsyndromic genes because obesity is the main phenotype brought about by the defective gene. Third, mice engineered by the transgenic and knockout technologies often are either obese or resistant to weight gain. These studies reveal that overexpressing or inactivating a gene often is accompanied by alterations in the

determinants of adiposity and weight gain (Robinson et al., 2000, Brockmann and Bevova, 2002). Human orthologs may be expressed variably and thus may contribute to the epidemic even though they have not been shown to be associated with human obesity yet.

On the other hand, the arguments against a defective biology as the cause of the current obesity epidemic are just as numerous. The Mendelian diseases and instances of nonsyndromic obesity due to known mutations are quite rare and account only for a small proportion of the number of obese individuals. Another common argument is that the human genome cannot have changed dramatically over the last decades, although the prevalence of obesity has.

Our current understanding of the role of specific genes to the risk of obesity remains incomplete. Some people have inherited a predisposition to be in positive energy balance for long periods of time; however, the prevalence of this predisposition in the population is not known at this time. Those with a predisposition presumably were able to keep a relatively normal weight in a restrictive environment when food was less abundant and significant physical labor was necessary to obtain food and water to survive. However, in the current “obesogenic” environment—characterized by the availability in abundance of energy-dense foods and by low demands for physical activity—these individuals are fighting a constant battle (Ravussin and Bouchard, 2000). Large numbers of those predisposed to obesity are losing this battle, as shown by the recent prevalence data in children and adults. In contrast, other people appear to have a low predisposition to obesity. Indeed, for a

substantial fraction of the population, an obesogenic environment has thus far not proven to increase their risk of obesity.

Thus, one can hypothesize that there are at least four broad categories of obesity risk. First, there are those who are obese because of a single defective gene. Second, another group is at risk of becoming obese as a result of a strong inherited predisposition mediated by subtler variation in a larger number of genes. Third, a large segment of the population has a genetic/developmental predisposition but will not become obese unless they live in an obesogenic environment. A last group is composed of individuals who are resistant to increased adiposity even in obesogenic environments.

In summary, 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. They will require large sample sizes, extensive phenotyping, longitudinal observations, and high-throughput DNA and gene-expression technologies. Genetics and proteomics, microarrays, transgenic models, knockout and knockdown models, comparative genomics, dense SNP panels, haplotypes and other relevant technologies will also be necessary if progress is to be made. One 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.

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

### **Adipose Tissue Biology**

Adipose tissue is a secretory organ that releases a number of hormones and cytokines including angiotensinogen, PAI-1, leptin,

adiponectin, resistin, TNF- $\alpha$ , IL-6 (see figure 4). These secretory products from the adipose organ are important as they have an impact on CVD, pulmonary, and other disease risk.

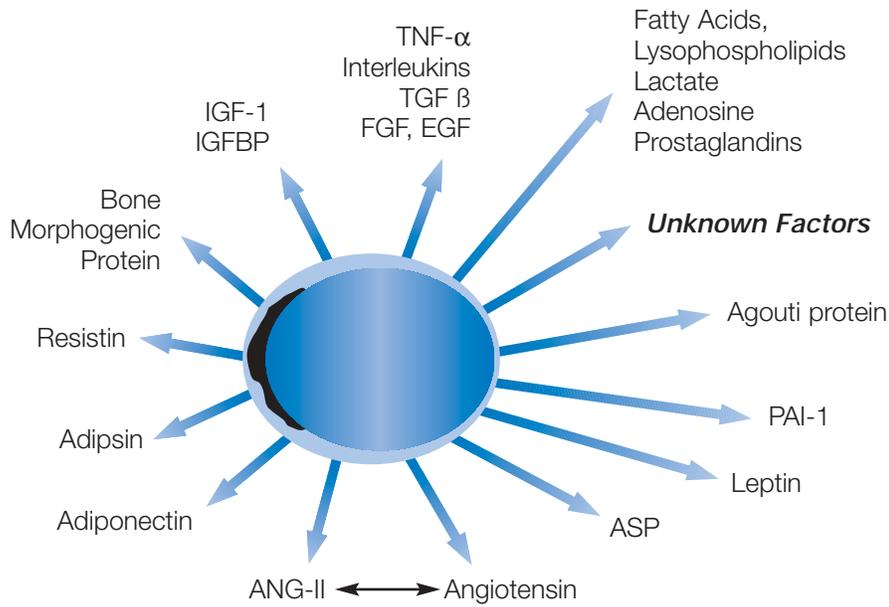
The regulation of adipocyte development, adipose-tissue volume, and adipose-tissue distribution is only partially understood (Eckel et al., 2002). Although scientists recently have learned much about the molecular events regulating adipogenesis, the picture is still incomplete (Mueller et al., 2002; Rosen and Spiegelman, 2000). The developmental, endocrine, and nutritional triggers for preadipocyte proliferation and differentiation in different depots in animal models and humans remain to be elucidated.

A better understanding of the regulation of the synthesis and secretion of these hormones and cytokines by adipose tissue is needed. In particular, it is not clear whether they all are secreted by adipocytes or if the stromal vascular fraction also is involved. Metabolic differences have been reported between abdominal visceral adipocytes and subcutaneous fat cells (Fried and Ross, 2004; Montague and O'Rahilly, 2000; and Rajala and Scherer, 2003)—thus, these must be characterized more fully. Moreover, it is unclear whether these depot differences are due to intrinsic adipocyte factors or are secondary to innervation, blood flow, or undetermined metabolic or paracrine factors. Finally, the relationship between adipose tissue cytokines and systemic inflammation are not well-understood (Eckel et al., 2002).

In summary, given the critical role of the adipose organ in human obesity and its comorbidities, including diseases of interest to NHLBI, a major research effort to increase our understanding of the biology of the adipose tissue is warranted at this time. A comprehensive program is needed to investigate how adipose tissue is regulated and why it is defended, the mechanisms of human variation in adipose-tissue distribution, the mechanisms of ectopic fat deposition and its relationship to metabolic

FIGURE 4

## Secretory Products of Adipose Tissue



Source: Reprinted by permission from the New York Academy of Sciences (Ravussin E, Smith SR. Increased fat intake, impaired fat oxidation, and failure of fat cell proliferation result in ectopic fat storage, insulin resistance, and type 2 diabetes mellitus. *Annals of the New York Academy of Sciences* 2002;967, Figure 4, page 371) copyright 2002 New York Academy of Sciences.

abnormalities, and the relationship between adipose-tissue cytokines and systemic inflammation.

### Nutrient Partitioning

The rates of fat oxidation at rest and under a variety of nutritional and energy balance perturbations are thought to be lower in those who are at a greater risk of gaining weight and becoming obese (Zurlo et al., 1990). However, the obese state is associated with enhanced rates of lipid oxidation thus normalizing the mixture of metabolic fuels oxidized in these individuals (Schutz et al., 1992). Whether a low-lipid oxidation rate under standardized conditions is a true risk factor for the development of obesity remains somewhat controversial. The partitioning of nutrients among organs and tissues under positive energy-balance conditions is only partially understood. Moreover, the mobilization of metabolic fuels among fat depots and other tissues and organs during periods of

negative energy balance or the demands of exercise at various intensities is not explained fully.

In summary, investigation is needed into the mechanisms regulating nutrient partitioning and fuel mobilization among tissues and organs in the normal weight, obese, and formerly obese given a variety of dietary practices, exercise levels, and energy-balance conditions. Also, the interactions between diet and exercise in the patterns of nutrient storage and metabolic fuel mobilization need careful experimental definition as little is known about them.

### Regulation of Food Intake

In normal weight individuals, day-to-day fluctuations in energy stores are detected and countered over periods of weeks and months, yielding stability in the amount of fuel stored as fat (Schwartz et al., 2003). Pathways that stimulate food intake and promote weight

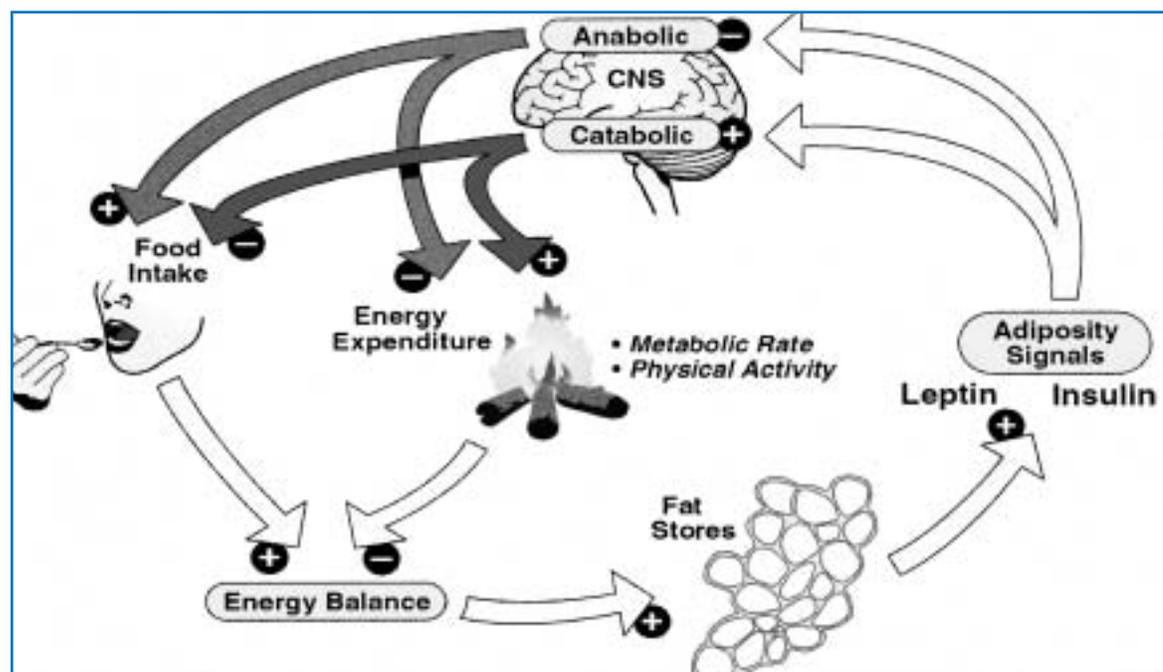
gain are defined as anabolic effector pathways (for instance, the NPY and AgRP neurons of the hypothalamic arcuate nucleus). In contrast, pathways that promote anorexia and depletion of body fat are known as the catabolic-effector pathways (e.g., arcuate nucleus melanocortin-producing neurons). When body-fat stores are threatened by food deprivation, robust responses are initiated to promote recovery of the depleted fuel stores. Such a response is a major obstacle to the successful long-term treatment of obesity.

How do these anabolic and catabolic pathways sense changes in energy balance? Leptin and insulin—hormones that circulate at concentrations proportional to body-fat mass—enter the brain and bind to receptors on target neurons. Both hormones are key candidates for the long-term regulation of anabolic and catabolic pathways. Obesity appears to be associated with impaired regulation of key neuronal systems by leptin and insulin as shown in figure 5 (Schwartz et al., 2000).

Certain short-term signals also participate in the regulation of food intake and body adiposity. Individuals experience satiety signals during meals as food interacts with receptors in the mouth, stomach, and intestine (Woods et al., 1998; Woods et al., 2000). For instance, the intestinal peptide cholecystokinin signaling is relayed to the hindbrain. As the meal progresses, the individual begins to feel a sense of fullness that contributes to the termination of eating. Therefore, understanding the interactions among short-term and long-term modulatory pathways on the regulation of body weight is a priority.

Research should focus on the mechanisms by which key neuronal systems become resistant to hormones regulating food intake and energy balance, how neuronal signals generated in response to input from adiposity-related hormones are transduced into changes of feeding behavior and autonomic function and how caloric flux and nutrients interact with satiety- and adiposity-related signals in

FIGURE 5  
Regulation of Energy Homeostasis.



Modified from Schwartz et al., 2000. Source: Reprinted by permission from *Nature* (Schwartz MW, Woods SC, Porte D, Seeley RJ, Baskin DG. Central nervous system control of food intake. *Nature* 2000;404, Figure 1, page 662) copyright 2000 Macmillan Publishers Ltd.

key neuronal subsets. Progress in these areas will play a major role in ongoing efforts to identify new targets for drug development.

## Fuel Regulation

Energy expenditure is a strong determinant of energy balance. It includes the energy expended in the basal state and at rest; the thermogenesis associated with the consumption, digestion, and storage of food and nutrients; and the energy expended for activity (Ravussin and Bogardus, 1989). The latter is important as it is the most variable component of daily energy expenditure. Although over the last decade much has been learned about the regulation of food intake, little progress has been made in understanding the regulation of metabolic rate and total energy expenditure. However, from what has been learned to date, it appears that while rodents have the ability to respond to increased caloric intake by increasing metabolic rate (adaptive thermogenesis); humans have a poor capacity to do so. Attempts to identify an adaptive thermogenesis component to augmented and sustained caloric intake over and above the gains in body mass thus far have yielded mixed and equivocal results. Several human studies have explored the relationships between resting-metabolic rate and weight gain over a number of years. Overall, the results are mixed, with some studies suggesting that low resting-metabolic rate was weakly associated with weight gain while others did not (Katzmarzyk et al., 1999; Saltzman and Roberts, 1995). Even though the data are mixed, in general, research indicates also that resting metabolic rate is not depressed in obese or formerly obese individuals when adjusted for variations in body composition.

These data contrast with those from physiological studies that show that the sympathetic nervous system can regulate metabolic rate through its effects on  $\beta$ -1,  $\beta$ -2, and  $\alpha$ -2 adrenoceptors. Data suggest that some obese subjects show increases in basal sympathetic nervous-system activity (van Baak, 2001). On the other hand, others have shown that parasympathetic activity is enhanced after

weight reduction while sympathetic activity is diminished (Aronne et al., 1995).

Similarly, there is little evidence concerning the effects of sustained caloric restriction or weight loss on the various components of energy expenditure. In one study (Leibel et al., 1995), body weight of normal-weight and obese subjects were reduced by 10 percent. They observed a decreased energy expenditure that was not accounted for entirely by the loss of body mass and lean mass. The greater-than-expected decrease in energy expenditure was thought to reside primarily in the nonresting component. Attempts to associate DNA sequence variants at candidate genes to energy expenditure phenotypes in humans thus far have yielded inconsistent results.

In summary, studies are needed on the development of new cost-effective methodologies to measure metabolic rate and energy expenditure in free-living people and on the molecular mechanisms regulating metabolic rates under positive and negative energy balance conditions. It also would be useful to develop new approaches for the study of the role of the autonomic nervous system in the etiology of obesity and in the defense of body-fat stores during weight loss.

## Critical Periods in Obesity Development

Identifying potential critical periods for the development of obesity is generating growing interest. A critical period is defined as a phase in life during which an individual may be at risk for an accelerated weight or adiposity gain. This higher risk may be caused by biological, behavioral, or prior life events. It is not known if the factors underlying various critical periods are similar or different. A number of periods throughout the lifespan have been proposed as critical periods. It has been proposed that fetal life entrains biological events that may increase the risk of developing obesity later in life as well as some of the metabolic anomalies commonly associated with obesity (Barker, 2002; Barker et al., 2002; Barker et al., 1993; Eriksson et al.,

2001, Li et al., 2001; Silverman et al., 1993; Silverman et al., 1995a; Silverman et al., 1995b; Pettitt et al., 1983). Birthweight commonly has been used as a surrogate for these fetal life exposures. Early infancy also has been recognized as one such critical period. The potential consequences of breastfeeding versus other feeding practices on subsequent weight gain has been recognized (Dietz, 2001). Early childhood is characterized by a surge in body mass relative to height. This so-called adiposity rebound phase has been defined as a critical period for the development of adulthood obesity by some investigators (Rolland-Cachera et al., 1984). Adolescence coincides with events that appear to relate to the risk of obesity. For instance, those who experience an early puberty tend to be heavier than those whose sexual maturation is delayed (Biro et al., 2001). Moreover, puberty is characterized by a transient insulin resistance that potentially may be related to subsequent risks for CVD and diabetes (Goran and Gower, 2001; Goran et al., 2003). In adult women, pregnancy is commonly associated with a greater risk of weight gain. The risk is more severe with repeated pregnancies (Rossner, 2000). However, in the CARDIA cohort, the weight gain increase was associated with the first birth only (Lewis et al., 1994; Lewis et al., 2000). In older women, menopause is associated with some weight gain, but also with more significant changes in body composition and in the partitioning of fat among body depots (Poehlman et al., 1995). Finally, dramatic changes in body composition occur as we age, with reductions in muscle mass and gain in adiposity (Gallagher et al., 2000; Janssen et al., 2000), although obesity is less prevalent with advancing age.

Most of the research to date has been observational and retrospective, for several reasons, the most compelling of which is that a long period of followup generally is needed between the critical period (exposure) and the change in body weight or adiposity (outcome). Another issue is that few studies have had a mechanistic focus. As a consequence, we know very little about the biological—genetically entrained or not—and environ-

mental factors that define a critical period for weight gain and are at the origin of the unfavorable outcomes.

In summary, the topic of critical periods is an area that would greatly benefit from the development of appropriate rodent and non-human primate models for study and from close interactions between basic science and clinical investigators. A major research effort is needed to understand whether prenatal, early postnatal, childhood, puberty, and adulthood critical periods truly entrain subsequent weight and adiposity gains and by what mechanisms. Whether weight and adiposity gains experienced during these critical life periods relate to the CVD morbidities associated with obesity also should be investigated.

## Diet and Physical Activity

### Dietary Intake

Obesity occurs only when energy intake exceeds total energy expenditure. Although macronutrient composition of the typical diet has received considerable attention over the last decade as a potential determinant of weight gain, most studies were short term. The energy density of food is probably an important determinant of energy intake. Research indicates that reducing the energy density of food by decreasing the fat content and increasing the water content through the addition of fruits and vegetables is associated with a spontaneous decrease in energy intake (Rolls, 2000; Yao and Roberts, 2001). Some studies have suggested that there is a hierarchy for the effects of the macronutrients on satiety: protein is the most satiating macronutrient and fat is the least satiating; however, whether the satiety features of macronutrients are important to energy balance is not yet clear (Bell and Rolls, 2001). The ready availability of a wide variety of palatable, inexpensive, energy-dense foods in large portions promotes excessive energy intake in the short term, but few data link these food-related variables to obesity (Bell and Rolls, 2001). Recent research has shown that portion size affects energy intake, but long-term studies are required to determine

whether the effect persists (Rolls, 2003). Epidemiological studies show that portions of many foods have increased in recent years (Nielson and Popkin, 2003; Smiciklas-Wright et al., 2003), but portion size has not been related to body weight directly.

The research on the effect of macronutrient intake on body weight is of particular interest in the present context. A prospective study found a correlation between fat intake and BMI (van Dam et al., 2002). Three meta-analyses of randomized trials have shown that a reduction in dietary fat leads to a decrease in total energy intake and to weight loss in studies lasting 6 months and more (Yu-Poth et al., 1999; Bray and Popkin, 1998; Astrup et al., 2000). A meta-analysis looking at long-term trials was inconclusive, due to the lack of long-term studies with continuous active treatment (Hill and Astrup, 2003). Recent studies indicate that reduction in dietary fat may affect weight loss because it reduces the energy density of the diet (Rolls, 2000; Yao and Roberts, 2001). However, no evidence exists to document that a lowfat diet is more advantageous for weight management than other types of diets when they are compared at the same total caloric intake (Bravata et al., 2003).

The data for carbohydrate content are mixed. No evidence exists to document that carbohydrates have any specific effects on body weight beyond their effects on energy density (Raben et al., 2003). Observational studies suggest that foods with a high glycemic index have a detrimental effect on BMI. However, intervention studies indicate that there is no significant effect of low glycemic index foods on weight loss (Pi-Sunyer, 2002; Raben, 2002).

Results from a 6-month controlled trial suggest that a high-protein diet (25 percent of calories) causes a greater weight loss than a lower (12 percent) protein content diet (Skov et al., 1999). Little is known about the contribution of energy intake derived from alcohol to obesity and weight management (Astrup et al., 2002). On the other hand, dietary calcium has been shown to be

involved in body-weight regulation in a limited number of studies (Zemel, 2003).

Although many studies have compared the effects of macronutrient composition of diet on weight loss, none has lasted long enough to draw conclusions about their merits for long-term weight control. Some studies show that a reduction in total fat, in combination with more fruit, vegetables, and whole grain foods, in combination with physical activity, produce a sustained weight loss (over 3 years), and reduce the incidence of type 2 diabetes and the numbers of cardiovascular events in high-risk subjects (DPP, 2002; Singh et al., 2002).

In summary, long-term randomized controlled trials on the effects of high- versus lowfat diets, high- versus low-carbohydrate diets, and high- versus low-protein diets on body weight and adiposity and on weight-related metabolic indicators are necessary to clarify the current controversies concerning macronutrient composition and weight control. Such studies require rigorous design and should last a minimum of 3 years, preferably 5 years or more. Moreover, studies on the effects of dietary calcium and dietary fibers and their effects on body weight should be undertaken. Finally, the effect of portion size on long-term energy intake needs to be determined.

## Physical Activity

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 is fueled also by the progressive decline in energy expenditure related to work and physical activity (Bouchard, 2000). Labor-saving devices, the use of personal cars for transportation even over short distances, and time spent watching TV, playing video games, and/or working or playing at the computer have had a considerable impact on the average daily energy expenditure (Kaiser Foundation, 1999). However, the exact decrease in energy expenditure over the last few decades and its contribution to the obesity epidemic have not been quantified.

Cross-sectional epidemiological studies have shown that indicators of inactivity are related to BMI levels. Moreover, a number of case-control and epidemiological studies have revealed that BMI and adiposity decrease and that energy expenditure increases in people who engage regularly in sports activities or who train for sports competition (Ross and Janssen, 2001). However, adding physical activity to a weight loss regimen generally does not lead to major additional weight loss. This is likely explained by the fact that many programs recommend a major decrease in energy intake but only a minor increase in energy expenditure of activity (Ross and Janssen, 2001). For instance, it is not uncommon for weight-loss programs to recommend a decrease of food intake of 500 kcal per day and a physical activity regimen requiring about 100 to 150 kcal per day, 3 to 5 days per week. Under such conditions, it is not surprising that physical activity does not contribute as much to the energy deficit as does dietary restriction. The dose-response relationship between energy deficit and weight loss is similar when the energy deficit is produced by increased physical activity as when produced by reduction in caloric intake (Ross and Janssen, 2001). Some studies suggest that physical activity plays a critical role in preventing weight regain once a significant weight loss has been achieved (Haskell, 1994; Hill et al., 2003). However, other studies have not observed these results (Blair et al., 1999; Saris et al., 2003).

Insufficient data are available to determine the amount of physical activity needed for the primary prevention of weight gain. However, this level of activity is likely to be moderate as suggested by recent estimates of the number of extra calories needed to gain about 2 pounds per year (Hill et al., 2003). Based on the observed distributions of weight gains in the CARDIA cohort (longitudinal) and the NHANES surveys (two cross-sectional timepoints), the average weight gain among 20–40 year olds is approximately 1.8 to 2.0 pounds per year. These estimates suggest strongly that the prevention of

weight gain and obesity could be achieved by relatively small increases in physical activity levels over current energy expenditure or commensurate change in calorie intake. However, this strategy remains to be tested experimentally.

When physical activity is added to a dietary or pharmacotherapy weight-loss program, it is thought that there is a greater preservation of lean mass; that is, a higher proportion of the weight loss is from adipose tissue (Ballor and Poehlman, 1994). This phenomenon may be even more pronounced when weight or resistance training is part of the weight-loss program (Donnelly et al., 1993). There is no convincing evidence that regular physical activity is associated with the prevention of increases in abdominal visceral fat or any other specific fat depots with age or with the loss of fat in such specific depots (Ross and Janssen, 1999).

An important question is how beneficial regular physical activity is for obese individuals who exhibit the features of the metabolic syndrome and of insulin resistance. It has been shown that overweight or moderately obese men and women who are moderately fit have a lower death rate from CVD and have a more favorable metabolic profile than the unfit overweight or moderately obese men and women (Lee et al., 1999). Whether this effect in obese people is as strong with regular physical activity as it is with fitness level remains controversial. It is also not known if the same metabolic benefits apply to obese individuals with BMIs greater than 35.

In summary, research should be undertaken on the support of the development of technologies designed to measure physical activity-related expenditures in free-living people over long periods of time (weeks), to investigate if there is better coupling between energy intake and expenditure at increasing levels of physical activity, to define the amount of physical activity necessary for the prevention of weight gain with age, and to study the impact of regular physical activity on

manifestations of the metabolic syndrome at increasing levels of BMI. The issue of the value of physical activity to prevent weight regain needs to be further explored in controlled trials conducted for longer periods of time than currently available studies. Clearly, further research is necessary to clarify the role of small changes in physical activity in weight control, in order to provide a firm basis for public health recommendations. Long-term studies with imaging technologies must clarify fully the effect of physical activity and weight training in body composition during weight loss and to identify the most favorable physical activity prescription to achieve the greatest preservation of lean body mass.

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

Obesity is encouraged by unfavorable environmental conditions—i.e., conditions that promote overeating and inactivity. For example, genetically similar populations may have no obesity or extremely high rates of obesity depending on differences in their environments (Ravussin et al., 1994).

The recent U.S. and global trends of increasing obesity in both children and adults suggest that such obesogenic environments either already are entrenched or emerging in most populations (WHO, 2000; Ebbeling et al., 2002), reflected in a “shifting” phenomenon in the entire BMI distribution and suggesting a populationwide etiology (see figure 6).

Changes in available foods and in activity environments, although not the only causes, must be considered the primary contributor to the rapid growth in obesity prevalence.

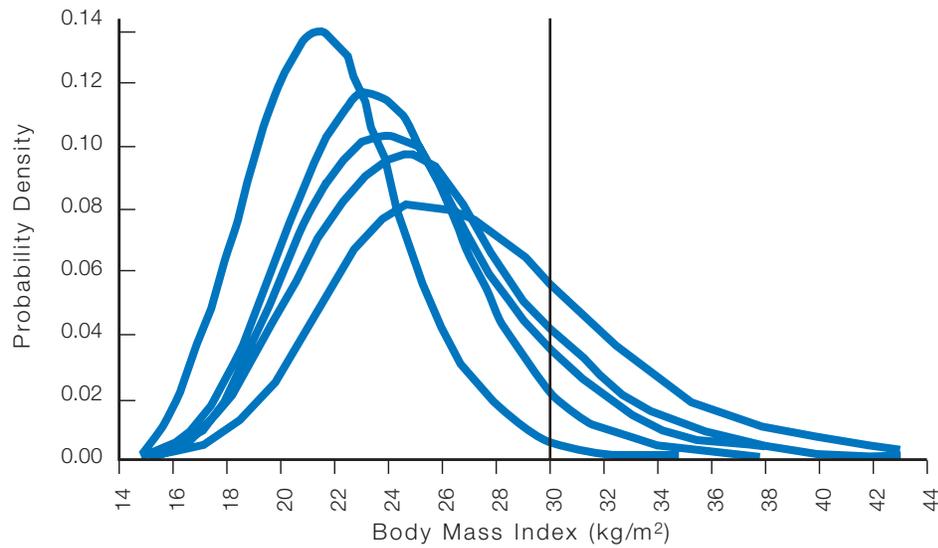
Lowering the relevant burden of environmental risks will be extremely challenging. Many of the contributory environmental conditions are derivatives of and anchored within patterns of urban and suburban community design, mechanization, employment, economic and marketing trends, and related changes in population lifestyles (Kumanyika et al., 2001; 2002b). The environmental determinants of aggregate health risks that are reflected so visibly in population weight trends are common to cardiopulmonary diseases, diabetes, and other major chronic noncommunicable diseases as well (Kaplan and Lynch, 1999). Hence, research to ameliorate environmental influences on obesity will complement other efforts to address diseases of interest to the NHLBI.

The far-reaching environmental and societal forces implicated in the obesity epidemic have been characterized as part of a “casual web” (Kumanyika et al., 2002b), a conceptual framework that arrays the relevant variables to suggest causal pathways (see figure 7). This causal web depicts pathways through which certain inescapable forces in the society at large determine individual eating and physical activity behaviors. These forces include economic development, globalization of media and marketing, and vertical and horizontal processes in multiple sectors across multiple levels. Many of the pathways are outside of the nutrition, health, and agriculture sectors that would seem to be most directly relevant. Also, as shown, vertical integration across different sectors that influence eating and activity behaviors is sometimes lacking, meaning that the convergence of influences on individuals may not be harmonious either with each other or with health and nutrition goals.

Attempts to intervene in obesity-related behaviors at the population level must inevitably consider this complex web of determinants. To do so within the framework of biomedical research will be a significant challenge. Some recent work provides more detailed frameworks for beginning to explore

FIGURE 6

The shifting distributions of BMI of five population groups of men and women aged 20–59 years derived from 52 surveys in 32 countries.



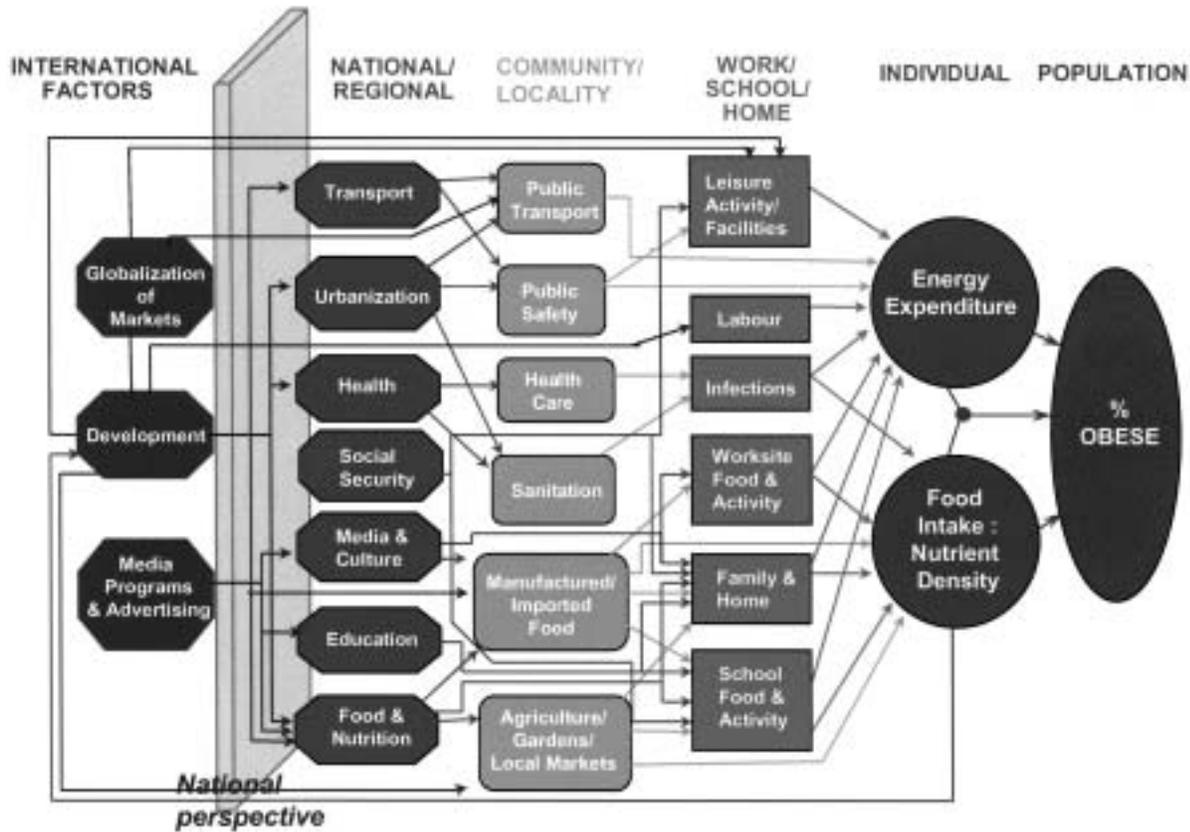
Modified from Rose, 1991. Source: Reprinted by permission from Springer-Verlag (Rose, G. *Population distributions of risk and disease. Nutrition, Metabolism, and Cardiovascular Diseases* 1991;1, Figure 1, page 38) copyright 1991 Springer-Verlag. Permission for the above work/extract to be adapted and reproduced for the figure granted from BMJ Publishing Group (Intersalt Cooperative Research Group. *Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. British Medical Journal* 1988;297:319-328, data from Appendix 1) copyright 1988 BMJ Publishing Group.

specific variables within these environmental and societal influence pathways (Booth et al., 2001; Dietz and Gortmaker, 2001; Davison and Birch, 2001; Swinburn et al., 1999; Goetz and Caron, 1999). Figure 7 is an example of a framework for thinking through macrosocietal pathways. These pathways can provide a basis for beginning the research necessary to determine which strands can be shifted more easily, which are more difficult to shift, and how much change really is needed to influence obesity rates in a beneficial direction. An example of the specification of layers of influence that might be operating at the microenvironmental of the home and family is provided in figure 8 (see the section on The Family Environment, page 41). A framework for systematic consideration of specific behaviors (“fast food” consumption or soft drink consumption) is provided in the following section on Environmental and Societal Influences on Food Intake (see page 38). Equally important to this line of research are attempts by others to articulate methodologies appropriate for assessing environmental and societal variables and for evaluating interventions in this domain (Richter et al., 2000; McKinlay, 1992; McQueen, 2001).

The opportunities are unprecedented, but the sheer complexity of societal determinants of obesity and their interactions suggests that relying on population BMI or obesity change as the only significant outcome may not always be the right choice. Relying on population BMI change may lead us to falsely reject programs that are successful in improving BMI-related determinants, but too distally for the results to yield population-wide BMI change in the short term. The research challenges are to begin to build up the database by focusing research at many different levels of the web, and to encourage a diversity of approaches where a strong underlying conceptual model has been articulated clearly. In addition, using tobacco as an example of population-level efforts to reduce the risk of cardiopulmonary diseases, lobbying for legislation, changing regulations, and advocating for policy might be the most effective means of creating a public environment that fosters rather than undermines healthy living, helps parents raise healthy children, and encourages institutions such as schools, Federal food programs, and the media to help change the food and lifestyle landscape. Research on policy and

FIGURE 7

**Causal Web of Societal Policies and Processes Influencing the Population Prevalence of Obesity.**



Modified from Kumanyika et al., 2002. Source: Reprinted by permission from Nature Publishing Group (Kumanyika S, Jeffery RW, Morabia A, Ritenbaugh C, Antipatis VJ. Public health approaches to the prevention of obesity (PHAPO) working group of the International Obesity Task Force (IOTF). Obesity prevention: the case for action. *International Journal Obesity and Related Metabolic Disorders* 2002;26(3), Figure 9, page 430) copyright 2002 Nature Publishing Group.

subsequent change in policy itself will be necessary to reduce prevalence.

Clarifying the causal pathways whereby environmental factors at different levels influence obesity development is imperative for understanding 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 operate, identification of appropriate methods for monitoring these influences and for incorporating them into interventions,

and assessment of relevant group- and individual-level outcomes. In addition, many environmental- and policy-level initiatives that are relevant to eating and physical activity patterns are being implemented, or will be implemented in the near future, spontaneously at the Federal level or in States and localities. Mechanisms must be developed to ensure the timely evaluation of the effects of these initiatives on caloric intake or expenditure, and to understand related changes in cardiopulmonary risk factors in individuals and populations.

## Environmental and Societal Determinants of Food Intake and Physical Activity

### Food Intake

Research on population food intake characteristics relevant to obesity has been largely descriptive, establishing the concept of “passive over-consumption” due to several related trends in food marketing and consumer behavior (e.g., increases in food and beverage portion sizes, increased consumption of sweetened beverages, food advertising on television) including the possibility of targeted marketing of high-energy, low-nutrient-dense foods to African Americans (Tirodkar and Jain, 2003), the proliferation of fast food outlets, the lack of supermarkets or other indicators of limited availability of healthful foods in inner cities, and the increasing consumer dependence on food eaten or purchased away from home (Cheadle et al., 2000; French et al., 2001; Morland et al., 2002b). Some of these factors have been linked to individual behavior either through observational studies or experiments (Coon et al., 2001; Borzekowski and Robinson, 2001; Morland et al., 2002a; Rolls et al., 2002; Ebbeling et al., 2002). In addition, some intervention studies have demonstrated the responsiveness of consumer behavior to environmental changes, such as in pricing and in the types of food available in cafeterias and vending machines in schools or worksites (French et al., 2001; Ritenbaugh et al., 2003). The latter study (Ritenbaugh et al., 2003) demonstrated significant changes in insulin levels suggesting a biological as well as a behavioral response.

The need for systematic attempts to understand the nature and strength of specific environmental influences in relation to individual biological and behavioral regulatory systems is critical. In other words, we need to know how to move from the macrosocietal level, through microenvironments, to individual behavior. To further show the nature and potential feasibility of studying some of these relatively complex topics, some examples

include how one might deconstruct an outcome such as soft drink or fast food consumption for pursuit in epidemiological, laboratory, or intervention research, as appropriate to the question of interest. Relevant variables relate to psychobiologic factors (e.g., palatability), social and cultural norms and values (e.g., fads, trends, pleasing children), the settings in which behaviors occur (e.g., car-based culture, vending machines), point-of-purchase or point-of-choice issues (e.g., advertising, price), and larger societal issues (e.g., single-parenting, commuting, television, multinational food companies, consumer rights, advertiser rights). For example research on soft drink consumption might address:

- Physiologic state and differences in relation to appetitive hormones by age, gender, and genetic background
- Compensatory mechanisms when noncaloric substitutions are made
- Values that promote soft drink consumption
- Perceived barriers and benefits of switching to water
- Management of children’s requests for highly sugared products
- Methods for dealing with potential income losses to soft-drink enterprises
- Ways to change the local culture for soft-drink consumption
- Identification of stakeholders

Hypothesis-driven research is needed to support policy and social structural changes. Such research requires systematic observations (quantitative or qualitative) in both laboratory and natural settings in order to assess relationships among sets of key environmental and societal variables that influence obesity. Although it is critical to conduct research to identify specific eating behaviors that respond to environmental manipulations, it also must be recognized that such changes, in isolation, do not necessarily influence BMI over the short term. Informative behavioral or biological intermediates are needed for short-term studies. Comprehensive studies in which multiple

levels of environmental determinants of obesity are altered over the long term may be needed to demonstrate BMI changes. More general types of pertinent questions in this research domain might include the following:

- Are there environmental contexts which promote overeating? If so, what are the characteristics of those contexts? What describes people who are able to avoid overeating in these situations?
- Is there a threshold of environmental food availability above which individual appetite regulatory mechanisms are overwhelmed?
- In the current environmental circumstances where food is abundant, are human appetite regulatory mechanisms geared to prevent starvation but not to curb overeating?
- In general, given the strong and persistent environmental predispositions to overeating, why have some individuals not become obese as yet?

## Physical Activity

Numerous environmental factors that facilitate or limit physical activity have been identified, conceptually (Booth et al., 2001; Sallis et al., 2002), in observational studies (Handy et al., 2002; Humpel et al., 2002; Berrigan and Troiano, 2002), and in intervention studies (Kahn et al., 2002). Urban design supporting high-population density, high-street connectivity, and mixed land use is associated with increased physical activity, because it allows people to walk to destinations that are in close proximity to their residences. Conversely, urban sprawl (urbanized areas with separate land use areas and automobile dependency) is associated with decreased physical activity, increased BMI, and higher rates of a variety of chronic medical conditions, including hypertension, arthritis, breathing difficulties, and heart disease. Fear of crime has a negative association with physical activity because it discourages people from walking in neighborhoods and parks. In addition, at least theoretically, aesthetics of neighborhoods/parks may be related to physical activity levels.

Research in this area has been encouraging regarding the ability to influence individuals' physical activity levels through environmental changes (Kahn et al., 2002). Studies have shown that increasing access to physical activity through organized, structured, and supervised activities is effective for youth and adults; that providing access to exercise equipment and walking/biking trails also is associated with increased physical activity; and that increasing awareness of physical activity opportunities (e.g., point-of-decision prompts at stairways) is effective in promoting physical activity. Community-level interventions that use a variety of interventions are effective—especially in the areas of communication and opportunities for activity. However, outside of prompts to be more active at the point of decision (e.g., “take the stairs”) media strategies alone may not be effective.

Changing the nature of physical activity determinants requires undertaking nontraditional (from a biomedical research perspective) approaches and partnerships. For example, partnerships with the transportation sector can be developed to evaluate the impact on physical activity, obesity, and other health outcomes of Federal highway and transit spending and on State and local efforts to make cities walkable and bikeable. Through partnerships with departments of parks and recreations, researchers can evaluate local, State, and Federal spending on parks and recreational facilities and their impact on physical activity and obesity. Partnerships with employers and with the Department of Labor and the Occupational Health and Safety Administration will enable the evaluation of the impact on physical activity, BMI, and other health outcomes of building design/workplace design and workplace policies including break time and performance demands of sedentary occupations. Research partnerships with the Department of Housing and Urban Development and with local agencies can enable studies to evaluate the impact of urban designs and housing developments, zoning and land use on physical activity and obesity. Finally, such

partnerships with local parks, agency departments, and school boards (for after-hours facilities access) can encourage the development and testing of organized community-based adult sports/activity programs as a preventive approach to obesity.

Physical activity opportunities are determined outside of the traditional health sector. A forum should be established to foster interchange with key agencies. Relevant agencies and organizations include those involved with transportation, housing, land use, urban design, and occupational health and safety, to name a few.

### The Family Environment

The family and home are critical microenvironmental settings influencing individual eating and physical activity behaviors, particularly for children. Obesity runs in families, and obese children usually have parents and/or siblings who are obese. The family environment may be shaped by biological, psychological, social/environmental, cultural, and behavioral factors (Epstein et al., 1998; Goetz and Caron, 1999; Davison and Birch, 2001; Dietz and Gortmaker, 2001). Theoretically, multiple routes exist whereby families may promote or inhibit the development and maintenance of obesity and these too have been identified in conceptual frameworks that not only list specific variables of potential interest but also indicate how these variables interrelate. For example, figure 9 shows several specific variables to be considered, organized within the layers of the community and neighborhood, parenting styles and family characteristics, and child characteristics and risk factors. Logic models for influences in childhood energy balance have been proposed for both family and school settings (Dietz and Gortmaker, 2001). Many potentially modifiable family environment factors have been identified in observational and laboratory-based research.

Parents and children not only share genes (unless one or more children is adopted) but they also share a common environment that can shape eating and exercise patterns.

Relevant influences include food access, meal patterns, child feeding practices; the role of food in social interactions and interpersonal transactions among family members—including the use of food for reward or punishment or to express caring; norms and values related to food; levels and types of activity and inactivity; social eating occasions; schedules; modes of transportation; entertainment media; and recreation patterns. Family members model eating and activity behaviors for each other, influence body image, and provide positive or negative social support for weight-control efforts. Parent-child influences on weight-related behaviors are bidirectional. Children influence the attitudes and behaviors of their parents and other family members. The receptivity of children to media, technology, and advertising may be a conduit for obesogenic influences on the entire family (Sobal, 2001). Intervention strategies in which children are the delivery agents for family health promotion messages suggest also that child-to-parent influences can be leveraged constructively from a lifestyle-change perspective (Epstein et al., 1994; Epstein et al., 1990).

Family interventions to prevent obesity have been implemented in school settings, face-to-face with individual families or groups of families in their homes or communities, and without direct personal contact, through mediated communication (e.g., phone, video, written materials) (Robinson, 1999; Robinson and Killen, 2001; Luepker et al., 1996; Perry et al., 1989). Generally these interventions produce 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 activities. Evidence indicates that many families do not like the inherent intrusiveness of face-to-face or group interventions, and most parents prefer interventions that can be completed in their own home, particularly if these interventions involve their children.

Family-based treatment of obese children targets multiple family members and



embedded within intervention trials—are needed to identify modifiable family-environment factors associated with obesogenic diets, activity, and sedentary behavior in both adults and children. Theory-based interventions that attend not only to the motivations and skills of all family members to adopt more healthful behaviors, but also to the willingness/ability of family members to participate in the intervention itself are essential.

## Prevention

In 2001, former Surgeon General Dr. David Satcher issued the *Call to Action to Prevent and Decrease Overweight and Obesity*, in which he identified obesity as the most important public health challenge we face in this country. Indicative of the state of the science at that time, Dr. Satcher commented that “the epidemic of obesity is relatively recent and unlike tobacco use, where we know enough to address the challenges, there is no substantial knowledge base for the prevention of obesity” (DHHS, 2001).

Although there is agreement that prevention of obesity should be of high priority a paucity of trial evidence makes implementation of this goal difficult. Researchers and others agree that children should be a major focus of prevention efforts, and most of the work done on obesity prevention to date has focused on children, often in school settings (Davis et al., 2003). In a recent review of the literature on interventions specifically designed to prevent obesity in childhood, only 10 studies the reviewers identified met their criteria, and only five of these showed significant results (Campbell et al., 2003). These researchers concluded that there is a lack of substantive evidence regarding the effectiveness of obesity prevention programs, and therefore, no generalizable conclusions are possible. Many carefully designed and comprehensive obesity prevention interventions have yielded disappointing results when evaluated by population-wide BMI changes, although these interventions may have been successful in influencing certain obesity-related behaviors (Nader, et al., 1999; Luepker et al., 1996). Some evidence exists that a

concentration on strategies that encourage the reduction of sedentary behaviors and an accompanying increase in physical activity may be fruitful (Campbell et al., 2003; Steinbeck, 2001). However, well-designed studies that examine a range of interventions on behaviors and environments that contribute to obesity development remain a priority.

In spite of the vast amount of research on obesity treatment, obesity prevention is only now being defined as a major research and policy focus (Kumanyika, 2001; Kumanyika et al., 2002b; Swinburn and Egger, 2002). Many of the challenges of obesity prevention as a research endeavor already have been described in relation to the need to address the spectrum of macroenvironmental to individual determinants of food intake and physical activity. Specific challenges in obesity prevention research have been articulated by investigators funded under a NIH initiative sponsored by the NIDDK, NHLBI, the National Institute on Aging, and the National Institute of Child Health and Human Development to stimulate innovative pilot studies in the area of obesity prevention (NIDDK, 2003; Kumanyika and Obarzanek, 2003). These pilot studies have involved approaches to obesity prevention in both children (primarily outside of the school setting) and adults and used both population-based and high-risk approaches. Among the key gaps in the literature identified by the pilot studies investigators was that of understanding of population motivations for preventing weight gain as opposed to losing weight. These investigators also raised the question of whether the most effective approaches to prevention of weight gain were in the domain of general health promotion, i.e., of healthful eating and physical activity practices as opposed to high-risk strategies in which treatment approaches were used to cause cycles of weight loss or otherwise curb overall weight gain (Kumanyika and Obarzanek, 2003).

Future efforts must develop and sustain strong relationships with communities and engage them as partners in the process of

identifying the best prevention strategies (Davis and Reid, 1999). In this vein, the realities and limitations of public health, population-based prevention research must be recognized. New studies must focus particularly on the following aspects of design:

- Sufficient statistical power
- Adequate followup of participants
- Development of appropriate tools for measurements of eating and physical activity in field settings
- Reliability of outcome measurements
- Process indicators, especially how well the intervention was delivered
- Evaluation of cost-effectiveness
- Appropriate and adequate statistical analysis
- Sustainability
- Generalizability

From a methodological perspective, rigorous and innovative approaches other than randomized controlled trials should be considered for prevention research, as such trials are not appropriate for research in many natural settings and cannot incorporate the environmental and societal variables previously described.

Innovative programs that encourage reduction of sedentary behaviors and increased physical activity must be supported. Future studies should examine interventions that focus not only on the individual but on the environment, using an ecological approach and addressing social norms and public policy as well as behaviors. Efforts to prevent obesity should focus on children and adolescents as a high priority and continue to build the evidence base to determine the most cost-effective and efficacious health promotion strategies. A network of “community” obesity researchers—perhaps following the model of existing research networks and community coalitions—must share observations, tools, problems, and successes in order to inform the next generation of studies and improve/adjust causal models.

## Treatment

The spectrum of obesity treatment includes traditional calorie-reduction programs combined with physical activity that produce modest weight loss, more restrictive calorie reduction approaches that produce greater weight loss, and more invasive interventions such as pharmacological therapy and bariatric surgery. As summarized in the *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults; The Evidence Report* (NHLBI, 1998), a comprehensive program of diet, exercise, and behavior therapy induces a loss of approximately 7–9 percent of initial weight in 6 months. Two FDA-approved medications—orlistat and sibutramine—also induce losses of 7–10 percent (when combined with a modest program of lifestyle modification). Surgical interventions, by contrast, induce losses of 25–30 percent of initial weight. Large, multisite randomized trials have shown the benefits of modest weight loss in reducing blood pressure (Stevens et al., 1993; Stevens et al., 2001; Kumanyika and Iqbal, 2003) and the risk of developing type 2 diabetes (Knowler et al., 2002). These and other trials (Kelly et al., 2002) have revealed several areas for further research.

The best dietary approach to treat obesity and sustain successful long-term weight loss is not known. Many dietary factors have been shown to affect total energy intake (Klein et al., 2002). They involve:

- Macronutrient content (carbohydrate, protein, fat), energy density (calories per gram of food), fiber, meal replacements, food substitutes (intense sweeteners, fat substitutes), portion size, and food variety
- Factors affecting the acquisition of food, such as availability, cost, and advertising
- Behavioral issues involved in enhancing dietary compliance, such as providing a simple and structured meal plan

Identifying the dietary components that can affect overall energy intake by enhancing satiety (increased feeling of fullness during a meal) and satiation (decreased feeling of

hunger between meals) requires further study. Several dietary approaches have shown beneficial effects in achieving weight loss: lowfat diets (Astrup et al., 2000), low energy-density diets (Stubbs et al., 1998), low-carbohydrate diets (Brehm et al., 2003; Foster et al., 2003), and high-protein diets (Skov et al., 1999). All support the need for additional long-term studies.

Weight regain remains the principal challenge in the treatment of obesity. Physical activity in the amount prescribed does not appear to be particularly effective for initial weight loss but is important for long-term avoidance of weight regain (Schoeller et al., 1997; Jakicic et al., 1999). New methods of facilitating the maintenance of weight loss are needed, as well as ways of inducing greater weight loss than has been achieved in the past.

Currently bariatric surgery is the only effective and sustainable therapy for extreme obesity and its comorbidities. The need to develop less invasive but effective therapeutic options does not obviate the need for research to improve the utilization of surgical therapy when it is appropriate. Surgery, because of the large weight losses it produces, provides a useful platform for various types of research, particularly in light of the different physiological states resulting from the various surgical procedures currently in use. One question that emanates from recent studies of bariatric surgery patients relates to the sustainability of CVD changes associated with large, sustained weight losses—e.g., for how long does maintenance of lost weight assure maintenance of reduced risk-factor status? (Sjöström et al., 2000). The role of diet in the maintenance of weight loss and reduced risk factor status should also be studied. Long-term studies on the effects of bariatric surgery-induced weight loss on mortality rates remain unavailable.

In summary, research needs on obesity treatment cover a wide area. In addition to research on identifying factors predisposing to weight regain and assessing whether such

factors are the same in children and adults, focused research is needed to improve obesity treatment outcomes in high-risk ethnic minority populations (Kumanyika, 2002c). A greater understanding is needed of cultural factors that influence treatment seeking and outcome, particularly given that success in obesity treatment appears to be less in ethnic minorities who experience higher-than-average prevalence of obesity than Caucasians (Kumanyika, 2002a; 2002c). Better pharmacologic therapies are needed, possibly including plant-based therapies (e.g., complementary and alternative medicine). Research to develop less invasive bariatric surgery procedures and to determine the long-term consequences of weight loss induced by these surgical procedures on hard endpoints would be desirable. New research is needed to identify those who will and those who will not benefit from bariatric surgery, to identify the most effective operations to prevent complications, and to identify the causes of weight regain after bariatric surgery. In addition, research is needed on behavioral and metabolic phenotypes that would inform providers which therapies (i.e., behavioral, pharmacological, surgical, or some combination) are best for an individual. Studies are also needed to identify specific effects of reduced energy intake, altered dietary composition, or increased physical activity on comorbidities that may be present, independently of their effects on weight loss, and the associated mechanisms of any such effects should be investigated. The mechanisms by which decreased energy intake and increased physical activity improve cardiovascular risk profiles should also be investigated. Related areas of interest are the effects on CVD risk factors and health outcomes of cycles of weight loss and regain and of dietary and physical activity/fitness improvements in obese individuals without weight loss. Related areas of interest are the effects of cycles of weight loss and regain and of dietary and physical activity/fitness improvements in obese individuals without weight loss on CVD risk factors and health outcomes.

## Applications to Clinical Practice and Community Settings

The treatment provided in clinical trials has been intensive and expensive, delivered by highly trained staff to selected patients, but there has been little study of the generalizability of these findings to primary care or community settings. The provision of obesity care in primary care settings is characterized by ‘clinical inertia,’ defined as the failure of health care providers to initiate or intensify therapy when indicated. Primary reasons for clinical inertia are a lack of education, training, and organizational systems in clinical practices aimed at evaluating and treating obesity; various practice barriers; and physicians’ attitudes of futility, lack of perceived benefit, and low-reward level. Despite the recommendations of national organizations such as the American Academy of Family Physicians and American Medical Association that recommended routine obesity screening and counseling, few patients are actually screened for obesity or receive counseling. The most significant practice barriers include lack of reimbursement, limited time, competing demands, and lack of provider training in behavioral counseling. In addition, related issues include a lack of proven approaches, a lack of tools that can be used in practice, a lack of proven practice systems that can reinforce obesity management, and possible patient factors related to obesity treatment seekings. The U.S. Preventive Services Task Force has concluded that there is insufficient evidence for or against the provision of low- to medium-intensity behavioral, dietary, and physical activity counseling in primary-care settings (U.S. Preventive Services Task Force, 1996). Promising office-based systems found to support behavior change include tools such as protocols, prompts, reminders, and treatment algorithms. However, clearly, three factors necessary for physicians to intervene include adequate recognition of obesity as a medical problem, a willingness to provide intervention, and adequate skills and resources to do so.

In community settings, obesity management programs might build upon first- and second-generation community CVD risk-reduction programs. First-generation programs include the Minnesota Heart Health Program, the Pawtucket Heart Health Program, and the Stanford five-city project (Winkleby et al., 1997). These community-wide CVD prevention programs targeted multiple CVD risk factors and behaviors including smoking, physical activity, blood pressure control, cholesterol reduction, and weight management, as well as CHD mortality risk. The studies used innovative strategies to achieve planned interventions, and lasted for 5–8 years. Joint analyses of the three U.S. projects showed no statistically significant differences in either the risk factors or the CHD endpoints between intervention and control communities. Despite the absence of change, these three studies provided useful lessons about the design, implementation, and analysis of community trials and the challenges of conducting community-based research that are applicable to obesity prevention and weight management.

The first-generation studies used theories of community health education, social learning, communication, social marketing, and community activation, as well as more traditional biomedical and public health disciplines. Second-generation studies, including the Nova Scotia Heart Health Program, have relied on these theories as well as on studies of participation and community development in the prevention of chronic diseases (MacLean et al., 2003). These theories lie at the core of the community-based participatory research model. This model emphasizes the need for inclusivity, the potential for sustainability and success in other areas of public health, particularly in the fields of infectious disease and maternal and child health.

Efficacy research (e.g., randomized controlled trials) is well controlled with strict inclusion and exclusion criteria. Due to the absence of such control in real-world applications, translation of efficacy studies is critical to

their usefulness. Identification of specific design principles for practical applications may increase the likelihood of successful application of research-based interventions. Such design principles should follow simple rules that help guide program administrators through the complexity of multilevel, multidisciplinary, multitechnology real-world applications. Recently, simple rules for translation efforts have been proposed, according to a design phase titled the “4 Ss,” an acronym that stands for **S**ize (of the desired effect), **S**cope (of the program), **S**calability (of the intervention), and **S**ustainability (of the program over time). In addition, the 4 Ss are linked to an impact phase denoted by the acronym “PIPE.” The PIPE Impact Metric, stands for **P**enetration (into the defined target population), **I**mplementation (of the work plan), **P**articipation (in the obesity intervention) and **E**ffectiveness (which describes the value of each success) (Pronk, 2003). With respect to a venue for translational research, health plans may provide unique opportunities for testing integrated systems of weight management and other behavior-related interventions (Pronk et al., 2002). Integrated systems, in this context, refer to systems that integrate obesity interventions with other risk reduction strategies as well as integration across multiple intervention settings (i.e., workplace, clinic, community) and multiple operational platforms (for example, workplace program referral to primary care to bariatric surgery and, subsequently, return to work). A key design feature of these systems is the “readiness to provide” services and programs according to an individual patient’s readiness to change.

In that overweight and obesity now affect more than 60 percent of the U.S. adult population and nearly 80 percent in some high-risk subgroups, such as African American women, obesity treatment no longer can be viewed as a specialty service but rather must reach the average patient or consumer routinely.

Hence, the next generation of obesity treatment research must be much better grounded in considerations of its potential for translation to reach diverse populations in common

clinical practice and community service-delivery settings. Participatory research may have a place in the management of overweight in the community, but achieving the full potential of the approach still requires much research and additional methodological development. Translational research using integrated systems for weight management should be tested in real world settings such as health maintenance organizations.

## Some Consumer and Professional Society Perspectives

Dialogue and collaboration with various consumer and professional constituencies is essential for developing effective practical ways to confront the obesity epidemic. Space limitations precluded including all these important constituencies and the following represent a sample of the groups that could have been included.

### American Academy of Family Physicians

Family physicians increasingly need effective and practical office-based tools to address obesity education, prevention, and treatment. Obesity is a chronic condition that can be addressed longitudinally rather than in single intensive interventions. Tools must be developed and tested or modified to work in ambulatory practice during short, recurrent visits. Obesity care must be provided longitudinally over a period of months or years if it is to be effective, and addressed during visits for health promotion, illness prevention, treatment, and monitoring of acute illnesses as well as visits for chronic conditions.

Furthermore, family physicians need tools that work in the context of the patients’ lives. Patients spend only a tiny fraction of their lives in our offices. Therefore, the community must be involved in stemming the risk of obesity. Just as we have formed community asthma coalitions, we need to know how to develop community obesity or healthy behavior coalitions to address diet,

activity, and weight management using the resources of schools, faith-based groups, job sites, and recreational facilities, as well as the health and health care community.

Critical areas of research for the family physician caring for people with obesity include:

- Tools to facilitate rapid assessment of diet, activity level, readiness to change, self-perception, and functional status. These assessments should guide development of a personalized management plan such as writing a short exercise prescription that fits the person's current activity level, resources and preferences. These tools must move from one-size-fits-all weight reduction programs to individualized plans to reduce an individual's health risks of obesity.
- A better understanding of the risks and stigma associated with obesity.
- Research should continue on the most appropriate metric for assessing obesity and associated risks. Is the height-adjusted weight (BMI) the appropriate metric for assessing increased risk or is excess weight and lack of fitness a better metric or BMI plus a specific body habitus?
- Family physicians need evidence-based clear and concise messages and effective methods to motivate change.
- Community physicians must have research results that describe the natural history of obesity and the most cost-effective windows of opportunity to intervene, which requires answering questions such as:
  - When is it most important to intervene?
  - When is it too late?
  - When is prevention effective?
  - What can we learn from intergenerational histories of obesity?
  - What are the risks and benefits of addressing different levels of obesity?

## American Heart Association

The American Heart Association (AHA) has developed numerous materials relevant to the area of obesity, including a scientific statement on obesity, insulin resistance, diabetes, and cardiovascular risk in children that appeared in *Circulation* during 2003. The group also produces pamphlets on low-calorie and heart healthy cooking and foods, conducts a wide range of activities, and provides numerous materials via the AHA Web site.

At the Prevention VII meeting on Obesity and Cardiovascular Disease, which was held in May of 2002, the following research needs also were identified:

- Identification of worldwide comorbidities of obesity
- Long-term longitudinal studies to examine whether risks of obesity for CVD and metabolic disease differ among population and ethnic groups
- Identification of specific factors associated with weight gain and with abdominal obesity
- Determination of whether effective weight loss interventions reduce CVD mortality and morbidity
- Development of strategies for the prevention of obesity
- Increase in the knowledge of the control of fat deposition and its relationship to disease risk
- Identification of why some individuals do not become overweight or obese
- How to translate improved knowledge into actual behavior change and lifestyle modification
- Assessment of the relative benefits of weight loss via reduced caloric intake versus increased physical activity
- Identification of age-dependent risk factors for obesity development
- Analyses of secular trends in birth-weight/gestation distribution
- Assessment of relationships between fetal growth and later obesity and comorbidities

- Assessments of relationships between maternal glycemia and diabetes/obesity/comorbidities in offspring
- Clarification of relationships between infant feeding and later obesity
- Cardiac, structural, and functional changes related to obesity
- Outlining of the role of insulin resistance and type 2 diabetes in the development of further obesity
- Explanation of the process of fat distribution in the development of obesity in adolescence and young adulthood
- Description of the patterns of dietary intake and physical activity across the lifespan and in diverse populations
- Definition of the sensitive periods for weight gain that may provide targeted periods for prevention efforts
- Identification of strategies for identifying those at risk for obesity-related comorbidities
- Definition of factors that predict weight loss and successful weight-loss maintenance across the lifespan
- Identification of prevention and treatment
- Determination of level of physical activity that will prevent obesity in children, adolescents, and adults
- Explanation of the effect of physical activities on obesity comorbidities
- Development of incentives to increase physical activity; environmental changes to increase physical activity
- Identification of variables and behaviors that should be targeted for weight control
- Evaluation of the efficacy and cost effectiveness of intervention and dissemination of programs
- Identification of specific foods or dietary components related to the development of diabetes
- Evaluation of the effect of portion size on energy intake and obesity
- Determination of factors that influence consumer choices
- Gene-gene and gene-environment causes of obesity
- Genetic and molecular mechanisms that confer resistance to obesity
- Mechanisms of altered energy regulation
- Mechanisms of target organ injury such as obesity-associated renal disease and cardiomyopathy, autonomic dysregulation, inflammation, and thrombosis in obese patients
- Adipocyte biology and the role of adipose tissue as a proinflammatory secretory organ
- Lipid metabolism and atherosclerosis
- Animal models of obesity and diabetes
- Cardiovascular consequences of obesity during childhood and adolescence
- Association of race/ethnicity and gender with obesity
- Psychosocial risk factors for obesity
- The development and evaluation of educational programs for weight control

### **American Society of Bariatric Surgery**

Many overt health risks are associated with morbid obesity. Clinicians and patients alike are frustrated by treatment failures and the growing problem of weight gain. Bariatric surgery is not a panacea, and there are some 30-day complications, such as pulmonary emboli and cardiac infections, as well as some technical problems that can lead to certain conditions associated with the procedure. In addition, certain concerns have been raised by those who perform the procedure regarding the rapid increase in the number of surgeries performed, at a cost of \$2.8 billion last year alone; in addition the surgery tends to increase the risk of malnutrition, and long-term followup is critical to ensure that patients do not become malnourished. Finally a lack of standards has resulted in the use of a range of procedures, some less safe and less effective than others, and data are inadequate regarding possible side effects of these various procedures.

NIDDK is funding seven bariatric surgery clinical research centers that will make a significant difference, and some participants

The AHA Task Force on Strategic Research Direction has identified obesity and other risk factors as a priority science topic and enumerated several areas as in need of specific investigations, including:

urged NHLBI to do the same. Additional opportunities for research in the clinical areas include developing a database to track the progress of those who have had the surgery and to identify problems before they arise and using the same rigor as pharmaceutical agents and medical devices to evaluate surgical procedures. Basic sciences research includes elucidation of why diabetes and asthma disappear in patients who have had the surgery. It is important that NHLBI encourage a synergy between basic scientists and clinicians, to promote a setting for the development of new ideas, and to fund human-subject research.

### **Council on Size and Weight Discrimination**

Weight prejudice continues to exist in our culture, and researchers are not immune to its effects. Unbiased research—free from personal assumptions on the part of health care professionals—must be conducted to ensure progress toward improved health for all people.

Controversy and many unanswered practical issues remain hallmarks of obesity research. For example, it is unclear that all overweight or obese people suffer from medical problems. It also remains unclear that weight reduction, even in those rare instances when it is permanent, improves long-term health outcomes or overall mortality. More effort needs to be put into finding those who are at risk due to weight-related conditions, and programs should be developed that are specific to the needs of these groups.

A great deal of energy is going toward medicalizing obesity treatment, and this should be re-evaluated. There does not seem to be any advantage to treating uncomplicated obesity through repeated doctor visits. This places a considerable lifetime financial burden on obese people without any indication that a physician can help any more than any women's magazine.

Perhaps the main controversy in obesity research is that clinical trials of weight loss do not separate the effects of diet composi-

tion change and exercise. A considerable body of evidence is beginning to show that exercise alone—even without weight loss—can have a beneficial effect on obesity comorbidities. Although weight loss may provide some additional benefit, considering the failure rate of dieting it may not be a realistic public health goal at the present time. Instead, an emphasis on healthy behaviors would be more productive, and studies that work toward removing the barriers to behavior change in the areas of nutrition and physical activity should be supported.

A pressing need exists for more research on such issues as whether sustained weight loss does lead to lower blood pressure, whether sustained health improvements and behavior change can occur without weight loss (using such models such as the *Health At Every Size* series), whether yo-yo dieting leads to atherosclerosis, and whether consumers delay diagnosis and treatment due to concerns and embarrassment about being weighed and lectured. Above all, we need approaches to prevention and treatment that don't demonize obese individuals and that allow each individual to reach his or her own personal potential for good health.

### **North American Association for the Study of Obesity**

The North American Association for the Study of Obesity (NAASO) is the largest member-based obesity organization in the United States and has, for the past 21 years, been dedicated to the study, prevention, and treatment of obesity. It publishes the journal *Obesity Research* and the electronic newsletter *Obesity*. NAASO has undertaken substantive advocacy and educational initiatives and has collaborated with NHLBI to develop the first evidence-based clinical guidelines on obesity.

Many clinical issues in obesity concern the organization including:

- Reimbursement for obesity therapy
- Certification of treatment providers

- Education and training of physicians, trainees, and other health care professionals
- Recognition of obesity as a chronic disease that causes other diseases
- Interaction and coordination of efforts with other societies

Advocacy issues that NAASO shares with other societies are the unification of obesity stakeholders, education of political leadership, education of the public, the removal of stigma and discrimination, the identification of fraudulent treatments, and fundraising.

Critical research issues for the future include:

- Increased funding for obesity research
- The development of focused clinical prevention and treatment studies
- Identification of mechanisms for organ system pathophysiology
- Clarification of the usefulness and benefits of bariatric surgery
- The conduct of research into combining traditional metabolism and endothelial and cardiac functioning
- The conduct of translational research
- The development of interinstitutional program projects
- The examination of the genetics of obesity and obesity complications

### **Cardiac Risk Prevention Center at Walter Reed Army Medical Center**

Just as the general public is facing the challenge of obesity, so too is the military. Furthermore, the current epidemic of obesity in children and adolescents will be reflected in future generations of military personnel. At present, CVD is the leading cause of death among service members aged 40 and older, for which obesity is a risk factor. The Army has conducted a number of studies that document the burden of obesity and address possible dietary and activity solutions. One critical study will determine whether stress management provides an additive benefit to exercise and diet in treatment of metabolic syndrome.

Challenges in obesity research that face the military include:

- Treating obesity as a chronic illness
- Providing long-term disease management for weight loss
- Developing better tools to assess diet
- Developing early interventions
- Improving patient education and screening
- Improving compliance for screening in a military population
- Mandating physical activity prescriptions that include worksite opportunities and lifestyle/leisure physical activities
- Improving access to better nutrition by decreasing portion sizes and access to low-cost, high-fat, energy-dense foods

Research opportunities within the military require:

- The development of effective models of care for military beneficiaries
- The testing of interventions to prevent and treat obesity
- The assessment of the impact of weight loss on both surrogate markers and hard endpoints for CVD
- The development of effective psychosocial techniques to improve adherence to lifestyle change interventions
- The identification of gene-environment interactions for better identification and treatment of individuals at-risk for obesity and its comorbidities

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

### Critical Research Needs

By design, Think Tank participants identified critical research needs in each topic area: obesity-related diseases and risk factors; biological and behavioral contributors to obesity etiology; social and environmental influences on obesity; and prevention and treatment strategies. The more than 200 research opportunities identified by Think Tank participants were synthesized into generic capstone research recommendations for priority emphasis and grouped according to the type of research approach in the

NHLBI research spectrum (shown in figure 9). These same recommendations are grouped according to topic in the Executive Summary.

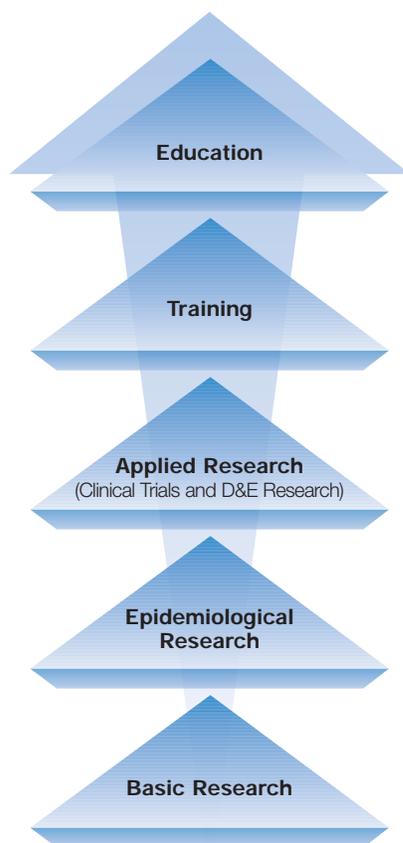
The use of the NHLBI obesity research spectrum reinforces the place occupied by basic and applied research in the concerted effort to employ a variety of disciplines and sciences to combat the obesity problem. It also depicts the role of integrated research and the need to ensure timely translation and implementation of research findings to the community. The research findings in each of the spectrum areas as well as implementation needs identified by the public inform and provide feedback into the research agenda reflected in the full spectrum of research opportunities for basic, clinical, epidemiological, and outcomes research.

The following recommendations were identified by the participants as being key areas for research emphasis. Some recommendations were combined to eliminate redundancy. To avoid a counter-productive competition for priorities across aspects of the NHLBI research spectrum, recommendations were grouped within categories of the spectrum. However, research approaches are not mutually exclusive and overlapping strategies can be used to target the same question. These recommendations should not be considered as being in any rank order.

### Recommended Priority Areas for Basic Research

- Pathophysiological mechanisms by which ectopic fat deposition increases the cluster of risk factors observed in the metabolic syndrome, and the risks for CHD, stroke, hypertension, asthma, and sleep apnea.

FIGURE 9  
NHLBI Overweight/Obesity Research to Education Spectrum.



- Mechanisms by which ectopic fat deposition occurs in skeletal muscle, liver, pancreas, heart, and other organs.
- Mechanisms by which obesity entrains the metabolic syndrome, and the specific impact of excess abdominal, subcutaneous, and visceral adipose tissue.
- Genes and sequence variants responsible for the predisposition to gain weight and become obese and for the fact that some obese persons develop associated morbidities while others do not.
- 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.
- 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.
- How adipogenesis and adipose tissue expansion are regulated and why adiposity is defended under negative energy balance conditions.
- 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.
- 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.
- 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.
- Molecular mechanisms regulating metabolic rates under positive and negative energy balance conditions.
- Mechanisms by which obesity affects the inflammatory process, neuroimmunologic function, and sympathetic nervous

systems in cardiovascular and pulmonary disease.

- 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.
- Genes and mutations responsible for the most consistent quantitative trait loci from genome-wide linkage scans for obesity.

### **Recommended Priority Areas for Epidemiologic Research**

- 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.
- 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; and consumers' ability to make informed food choices.
- Prospective observational studies to identify modifiable family environment factors associated with obesogenic behaviors, and the development of child and adolescent obesity.
- Associations of weight or adiposity gains experienced at critical life periods with subsequent obesity-related cardiovascular and other diseases in cohorts followed over time.
- The natural history of obesity and the optimal periods for effective intervention.
- Relationships between BMI or adiposity phenotypes and cardiovascular and pulmonary disease risk factors and events among ethnic groups.

- 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.
- Specific associations of acute and chronic poverty with obesity development and the related implications for other cardiovascular and pulmonary disease risks.
- Type of weight-loss diet that will produce a long-term weight reduction (e.g., weight maintenance for more than 5 years).

### **Recommended Priority Areas for Applied Research (Includes Clinical Trials, Demonstration and Education (D&E), and Translational Research)**

- Intervention research to determine ways to modify family environment factors associated with obesogenic diet, activity, and sedentary behaviors.
- 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) to 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, including attention to compensatory or displacement effects occurring outside of the system or organization.
- Amount of physical activity necessary for the prevention of excessive weight gain during developmental periods and in adulthood.
- 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.
- 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.
- 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.
- Long-term effectiveness of novel approaches to increasing regular physical activity in adults.
- Effects of recent changes in relevant government (Federal, State, and local) programs and policies on caloric intake and physical activity levels.
- Cost-effective, accurate methodologies to measure caloric intake and energy expenditure in free-living people.
- 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, and include studies of alternative methods of delivering treatment including the Internet, telephone, and media outlets.
- 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.
- Phenotypes of overeating and other variables that have implications for the design of obesity treatment programs and that characterize degrees of responsiveness to treatment.
- “Best Practices” related to obesity care and 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.
- Strategies for helping people to control the portions of the foods and beverages they consume independently of the portion size presented.

- 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.
- 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.
- Characteristics of persons resistant to obesity treatment in order to develop and target effective therapeutic approaches.
- 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.

### Recommended Priority Areas for Training

- 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, and 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 NIDDK obesity research centers, establish additional evidence-based centers that can serve as training and research centers for both new and established investigations.

## Summary

Weight status and the potential for excess weight to cause or aggravate heart, lung, blood diseases, and sleep disorders is a function of genetic, biological, and behavioral effects that occur within the contexts of myriad interdependent environmental and societal forces. Both fundamental research on environmental determinants of obesity and research on preventive and treatment interventions must be combined with research on variations in the underlying genetic and behavioral susceptibility to excess weight gain and obesity. Even when the environmental predispositions are considered overwhelming, not all individuals become obese or become obese to the same degree. Therefore, studies of genes related to energy homeostasis and the mediators of body mass and composition (energy intake, expenditure, and partitioning), in concert with studies of environmental influences, will be particularly informative.

Major research gaps exist with respect to all aspects of energy balance and the specific mechanisms whereby adiposity causes deleterious consequences on various target tissues. It is critical to understand the role of biology, because a key component of the obesity epidemic is the fact that this set of problems is dependent on biological predisposition. Similarly, studies of population-level interventions to decrease environmental facilitators of obesity will be most informative if they include individual level assessments of both biological and behavioral predispositions to weight gain. It is equally critical that obesity treatment research incorporate variables that can help to clarify treatment response subtypes on a genetic and phenotypic basis. Because families share genes, behaviors, and environments, family-based studies may offer particular advantages in this respect but need to be complemented by other designs.

Findings from the presentations on obesity-related comorbidities were designed to articulate some potential links between obesity research and emerging themes in the broader spectrum of research developments

relating to various heart, lung, and blood disorders, including metabolic syndrome, CHD, heart failure, asthma, hypertension and dyslipidemia, and sleep disorders. For example, high interest in understanding the functional implications and related metabolic consequences of fat deposition in nonadipose tissues for the risk of CHD has been expressed by researchers. Questions of interest related to the metabolic syndrome include the causal role of a sedentary lifestyle independent of obesity, differences by ethnicity, gender, and life stage, and the significance of metabolic syndrome for future cardiovascular events. Other questions can be framed in terms of mechanisms through which obesity induces specific risk factors such as low HDL-cholesterol or elevated blood pressure and why these mechanisms are not operative in some individuals. Numerous areas of research can be outlined in relation to obesity-related mechanisms that lead to heart failure and to asthma development. These are both areas in which research is limited. In the case of asthma, for example, it is important to understand the role of obesity-induced proinflammatory states or sympathetic nervous system changes. In regard to sleep disorders, studies on the causes of obstructive sleep apnea and the triggering mechanisms brought about by obesity are needed.

Available data are unable to explain how adipose tissue is regulated and why and how it is so well defended. We need clarification of why ectopic fat deposition occurs. A better understanding of neuronal and hormonal mechanisms regulating food intake and satiety—as well as the utilization of dietary energy from various sources—will help to identify potential new targets for the development of obesity treatment approaches, including drug therapies. Any advancement of the understanding of biological influences on energy expenditure levels is limited by the lack of cost-effective methodologies to measure metabolic rate and energy expenditure in free-living people and on the molecular mechanisms regulating metabolic rates under positive and negative energy balance conditions. Intervening regulatory

and metabolic processes that ultimately determine weight and body composition outcomes and their consequences must be identified. Research on the identification of the multiple genes and allelic variants responsible for the predisposition to obesity and its comorbidities should continue.

To develop a clearer basis for prevention of both obesity and its health consequences, all aspects of obesity development and progression need exploration throughout an individual's lifetime and across life stages both in human systems and, when advantageous, in appropriate animal models. For example, a major research effort is needed to understand whether prenatal, early postnatal, childhood, puberty and adulthood critical periods entrain subsequent weight and adiposity gains as well as whether and how weight and adiposity gains experienced during these critical life periods relate to CVD morbidities. Effects of specific types of changes in energy intake and physical activity also require systematic study—e.g., to clarify the effects on both obesity and complications of weight-loss diets with different composition, to define the amount of physical activity necessary for the primary prevention of weight gain with age, and to study the impact of regular physical activity on the manifestations of metabolic syndrome at increasing levels of BMI.

In addition to the basic and clinical research questions described, an urgent need exists to clarify the causal pathways whereby 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. The urgency relates both to the currently high population burden of and steep trends in obesity and to the inevitably slow moving nature of any corrective solutions that will be put in place once they are identified. Some environmental and policy-level initiatives that are relevant to eating and physical activity patterns are already taking place spontaneously at the Federal level or in States and localities. Hence, mechanisms are needed to ensure

the timely evaluation of effects of such initiatives on caloric intake or expenditure and on related cardiopulmonary risk factors in individuals and populations.

Efforts to prevent obesity should focus on children and adolescents as high priorities and continue to build the evidence base to determine the most cost-effective and efficacious health-promotion strategies. A network of “community” obesity researchers—perhaps following the model of existing research networks and community coalitions—must share observations, tools, problems, and successes in order to inform the next generation of studies and improve/adjust causal models. It is important to determine whether children show the same metabolic/behavioral responses to long-term weight reduction as do adults. With respect to arresting or reversing obesity and its consequences, high priorities for treatment research are to identify factors predisposing to weight regain, to assess whether such factors are the same in children and adults, to improve obesity treatment outcomes in high-risk minority populations, to develop better pharmacologic therapies, to conduct investigations of the long-term consequences for heart, lung, and blood disorders, and to determine the long-range effects of the relatively large and sustainable weight losses induced by surgical procedures.

Already, we have substantial evidence regarding environmental and behavioral determinants of obesity as well as the beneficial effects of certain types of interventions on CVD outcomes; now a pressing need for research is to refine our understanding of the practical relevance of these findings has emerged. 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 to obesity and, therefore, to viable hypotheses about where and how to intervene to prevent weight gain and promote weight loss and maintenance. Candidate variables or pathways may come from ecological studies (observations about aggregate variables,

including social structural changes) or from laboratory studies (findings based on manipulations of eating and activity determinants in experimental settings).

The high prevalence and related general population awareness of the problem of obesity present both an opportunity and a mandate to accelerate and enhance obesity research, particularly as it relates to CVD, the major cause of premature death and disability. The epidemic of obesity is a new challenge that requires an accelerated effort in order to expand the science base. Rapid translation and dissemination of all obesity research—from “bench-to-trench” and from “trench-to-bench”—should receive high priority to keep the prevention messages clear and consistent. The feasibility of linking with other Federal agencies both within and outside of the Public Health Service should be explored. Consideration should be given to creating (or to support existing) special-funding initiatives that foster and reward collaborations on obesity-related research among scientists in diverse disciplines and types of research. Phased funding mechanisms will be needed to permit solid grounding of community-based and multi-level research, in which the establishment of community level and environmental initiatives must precede development of interventions in embedded environments, such as schools. Attempts to intervene in obesity-related behaviors at the population level inevitably must consider a complex web of determinants, including many societal variables that are far beyond the traditional domain of biomedical research. The ultimate public health solutions will undoubtedly involve policies and processes that are outside of the control of researchers or research institutions. In this sense, these influences cannot be ignored by those who seek to identify ways to ameliorate the obesity epidemic and its health effects. The disease landscape is changing and is forcing changes in the research landscape, including the questions asked, the variables assessed, and the interpretations made. Perhaps no other public health challenge requires confrontation with change more than obesity.

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## Think Tank on Enhancing Obesity Research at the NHLBI

Bethesda Marriott Hotel  
Bethesda, Maryland

March 24–25, 2003

*Monday, March 24, 2003*

### Opening Remarks and Charge to Participants

8:00 a.m. – 8:10 a.m. **Claude Lenfant**, M.D., Director, National Heart, Lung, and Blood Institute, Bethesda

### Remarks From the Cochair

8:10 a.m. – 8:20 a.m.  
**Claude Bouchard**, Ph.D., Executive Director, Pennington Biomedical Research Center and Director, Human Genomics Laboratory, Louisiana State University System, Baton Rouge

**Shiriki Kumanyika**, Ph.D., M.P.H., Professor of Epidemiology and Associate Dean for Health Promotion and Disease Prevention, University of Pennsylvania School of Medicine, Philadelphia

### Overview

**Focus of session:** Set the stage for the think tank sessions by presenting an overview of past, current, and future aspects of the obesity epidemic from its relationship to cardiovascular disease (includes both coronary disease and hypertension and diabetes as a contributor), asthma and sleep disorders.

Comment: Should cover childhood aspects as well as adulthood aspects. Speaker or discussant should highlight implications for ethnic groups. Suggest research priorities.

8:20 a.m. – 8:40 a.m.

Overview: **F. Xavier Pi-Sunyer**, M.D., M.P.H. Professor of Medicine, Columbia University College of Physicians and Surgeons and Director, Obesity Research Center, St. Luke's - Roosevelt Hospital Center, New York City

8:40 a.m. – 9:00 a.m.

Overview: **June Stevens**, M.S., Ph.D., Professor of Nutrition and Epidemiology, University of North Carolina School of Public Health, Chapel Hill

9:00 a.m. – 9:10 a.m.

### Participant Dialogue

### Critical Life Periods

**Focus of session:** Review what is known and what we need to examine regarding the predictive factors that identify who is at most risk for increased susceptibility to weight gain and obesity. Describe what is known about the development of obesity throughout the life span and its effect on cardiovascular, pulmonary, or sleep disorder development and progression. Review the evidence for periods of life span when specific aspects of obesity (e.g., sleep deprivation, stress, rate of weight gain, duration of weight gain, fat patterning, weight instability, severity) appear to be most critical in the development of disease. Suggest research priorities.

9:10 a.m. – 9:30 a.m.

Overview: **Michael I. Goran**, Ph.D., Professor of Preventive Medicine and Physiology & Biophysics and Associate Director, USC Institute for Prevention Research, University of Southern California, Los Angeles

9:30 a.m. – 9:50 a.m.

Overview: **Stephen R. Daniels**, M.D., Ph.D., Professor of Pediatrics and Environmental Health, Children's Hospital Medical Center, Cincinnati

9:50 a.m. – 10:00 a.m.

### Participant Dialogue

10:00 a.m. – 10:10 a.m.

Break

### Genetics Overview

**Focus of session:** Review the evidence for a role of some genes and mutations in causing obesity and for the contribution of genetic factors in the more common forms of obesity assuming that the latter are determined by multiple genes interacting with a variety of environmental and lifestyle agents. Review which genes are important to human obesity including those that alter eating and physical activity behaviors, affect thermogenesis, and are associated with cardiovascular, lung, blood, and sleep comorbidities of obesity. Suggest research priorities.

10:10 a.m. – 10:30 a.m.

Overview: **Rudolph L. Leibel**, M.D., Professor of Pediatrics and Medicine, Head, Division of Molecular Genetics, and Codirector of the Naomi Berrie Diabetes Center, Columbia University College of Physicians and Surgeons, New York City

10:30 a.m. – 10:40 a.m.

Discussant: **Alan R. Shuldiner**, M.D., Professor and Head, Division of Endocrinology, Diabetes and Nutrition, Department of Medicine, University of Maryland, Baltimore

10:40 a.m. – 10:50 a.m.

### Participant Dialogue

### Adipose Tissue Biology

**Focus of session:** Review the evidence and identify the research priorities concerning the role of adipose tissue metabolism, fat mass, and ectopic fat deposition in obesity and the complications of obesity. Consider the metabolic interplay between adiposity and leptin, renin-angiotensin system, inflammation, oxidant stress, platelet activation and the potential effect on cardiovascular disease risk factors. Suggest research priorities.

10:50 a.m. – 11:10 a.m.

Overview: **Robert H. Eckel**, M.D., Professor of Medicine, Physiology and Biophysics, Division of Endocrinology, Metabolism and Diabetes, Department of Medicine, University of Colorado Health Science Center, Denver

11:10 a.m. – 11:20 a.m.

Discussant: **Susan K. Fried**, Ph.D., Professor, Division of Gerontology, Department of Medicine, Baltimore VA Medical Center, Baltimore

11:20 a.m. – 11:30 a.m.

### Participant Dialogue

### Regulation of Food Intake

**Focus of session:** Review the evidence concerning the central and peripheral mechanisms responsible for the regulation of food intake. Consider the potential role of the central and peripheral cardiovascular autonomic nervous system in mechanisms of appetite and satiety. Suggest research priorities.

11:30 a.m. – 11:50 a.m.

Overview: **Michael W. Schwartz**, M.D., Professor of Medicine and Head, Section of Clinical Nutrition, Division of Metabolism, Endocrinology and Nutrition, Harborview Medical Center and University of Washington, Seattle

11:50 a.m. – 12:00 p.m.  
Discussant: **Stephen C. Woods**, Ph.D.,  
Director, Obesity Research Center and  
Professor, Department of Psychiatry,  
University of Cincinnati, Cincinnati

12:00 p.m. – 12:10 p.m.  
**Participant Dialogue Overview**

12:10 p.m. – 12:30 p.m.  
Break

[Lunch Session: Implications of Obesity  
Research for Future Advances](#)

### Genomics and Proteomics

12:30 p.m. – 12:45 p.m.  
**Ronald M. Krauss**, M.D., Director,  
Atherosclerosis Research Center, Children's  
Hospital Oakland Research Institute and  
Senior Scientist and Head, Department of  
Molecular Medicine, Lawrence Berkeley  
National Laboratory, Oakland

12:45 p.m. – 12:55 p.m.  
**Participant Dialogue**

### Metabolic Syndrome

12:55 p.m. – 1:10 p.m.  
**Scott M. Grundy**, M.D., Ph.D., Professor of  
Internal Medicine and Biochemistry, Director  
of the Center for Human Nutrition, and  
Chairman of the Department of Clinical  
Nutrition, University of Texas Southwestern  
Medical Center, Dallas

1:10 p.m. – 1:20 p.m.  
**Participant Dialogue**

### Heart Failure

1:20 p.m. – 1:35 p.m.  
**Steve B. Heymsfield**, M.D., Medical Director  
of the Weight Control Unit, Obesity  
Research Center, St. Luke's - Roosevelt  
Hospital Center, Columbia University, New  
York City

1:35 p.m. – 1:45 p.m.  
**Participant Dialogue**

### Regulation of Energy Metabolism and Nutrient Partitioning

**Focus of session:** Review the evidence concerning our understanding of the regulation of basal metabolic rates, food-induced thermogenesis, other thermogenic components, and energy partitioning. Consider whether any aspects of energy metabolism or nutrient partitioning associated with obesity are also associated with increased cardiovascular disease risk and whether the risk is reversible with successful weight loss. Suggest research priorities.

1:45 p.m. – 2:05 p.m.  
Overview: **Susan B. Roberts**, Ph.D., Senior  
Scientist, Department of Energy Metabolism,  
USDA Human Nutrition Research Center on  
Aging at Tufts University, Boston

2:05 p.m. – 2:15 p.m.  
**Participant Dialogue**

### Dietary Issues

**Focus of session:** Review the new evidence on the role of energy and nutrient intake in the etiology of obesity, especially the role of dietary factors such as fatty acids, food volume, nutrient density, and protein versus carbohydrate intake. Review the role of optimal macronutrient composition on diet for weight loss, weight maintenance, and obesity prevention. Suggest research priorities.

2:15 p.m. – 2:35 p.m.  
Overview: **Arne V. Astrup**, M.D., Ph.D.,  
Professor, Department of Human Nutrition,  
Royal Veterinary and Agricultural University,  
Frederiksberg, Denmark

2:35 p.m. – 2:45 p.m.  
Discussant: **Barbara J. Rolls**, Ph.D., Professor  
and Guthrie Chair, Department of Nutrition,  
Pennsylvania State University, University  
Park

2:45 p.m. – 2:55 p.m.

### **Participant Dialogue**

2:55 p.m. – 3:05 p.m.

Break

### **Physical Activity**

**Focus of session:** Review the evidence for the role of physical inactivity and physiological mechanisms involved in the development of obesity. Consider new developments in exercise physiology, including the physiological role of cardiovascular and pulmonary adaptation to exercise in maintaining energy balance and fostering a healthful ratio of adipose tissue and lean muscle mass. Suggest research priorities.

3:05 p.m. – 3:25 p.m.

Overview: **James O. Hill**, Ph.D., Director, Center for Human Nutrition, University of Colorado Health Science Center, Denver

3:25 p.m. – 3:35 p.m.

Discussant: **William L. Haskell**, Ph.D., Stanford Center for Research in Disease Prevention, School of Medicine, Stanford University, Palo Alto

3:35 p.m. – 3:45 p.m.

### **Participant Dialogue**

### **Stakeholder Perspectives**

3:45 p.m. – 4:00 p.m.

**Robert O. Bonow**, M.D., President, American Heart Association

4:00 p.m. – 4:15 p.m.

**Barbara Yawn**, M.D., M.Sc., American Academy of Family Practice

4:15 p.m. – 4:30 p.m.

**Walter J. Pories**, M.D., President, American Society for Bariatric Surgery

4:30 p.m. – 4:45 p.m.

**Samuel Klein**, M.D., President, North American Association for the Study of Obesity

4:45 p.m. – 4:55 p.m.

### **Participant Dialogue**

4:55 p.m. – 5:00 p.m.

Announcements

5:00 p.m.

Meeting Adjourned

*Tuesday, March 25, 2003*

### **Family Environment**

**Focus of session:** Review the evidence for familial influences on obesity development during childhood, including evidence from family-based studies of obesity prevention or treatment. Suggest research priorities and types of study designs that would facilitate more effective interventions to ensure achieving and maintaining a healthy weight that includes the entire family.

8:00 a.m. – 8:20 a.m.

Overview: **Leonard H. Epstein**, Ph.D., Professor, Departments of Pediatrics, Social and Preventive Medicine and Psychology, Division of Behavioral Medicine, University of Buffalo, School of Medicine and Biomedical Sciences, Buffalo

8:20 a.m. – 8:30 a.m.

Discussant: **Thomas N. Robinson**, M.D., M.P.H., Assistant Professor of Pediatrics and of Medicine, Division of General Pediatrics and Center for Research in Disease Prevention, Stanford University School of Medicine, Palo Alto

8:30 a.m. – 8:40 a.m.

### **Participant Dialogue**

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

**Focus of session:** Review conceptual models for how levels and types of environmental and societal variables related to food intake act to influence obesity and the progression of cardiovascular and pulmonary disease and give specific examples of proposed causal

pathways; discuss the types of evidence for interventions that address elements of these pathways. Suggest research priorities.

8:40 a.m. – 9:00 a.m.

Overview: **Cheryl K. Ritenbaugh**, Ph.D., M.P.H., Senior Investigator, Department of Epidemiology and Disease Prevention, Kaiser Center Health Research, Portland

9:00 a.m. – 9:10 a.m.

Discussant: **Kelly D. Brownell**, Ph.D., Professor of Psychology and Director of the Yale Center for Eating and Weight Disorders, Yale University, New Haven

### Environmental and Societal Influences on Physical Activity

**Focus of session:** Review conceptual models for how levels and types of environmental and societal variables act to influence obesity and the progression of cardiovascular disease and pulmonary disease and give specific examples of proposed causal pathways; discuss the types of evidence for related interventions. Suggest research priorities.

9:15 a.m. – 9:35 a.m.

Overview: **Deborah A. Cohen**, M.D., M.P.H., Senior Natural Scientist, RAND Corporation, Santa Monica

9:35 a.m. – 9:45 a.m.

### Participant Dialogue on Food Intake and Physical Activity

9:45 a.m. – 9:55 a.m.

Break

### Prevention

**Focus of session:** Review current and recent research in progress under the banner of obesity prevention, the current thinking about models for obesity prevention, including some comments reacting to the deliberations of the Obesity Pilot Studies Workshops, e.g., how it should be defined, how research in this area should be approached. Suggest research priorities.

9:55 a.m. – 10:15 a.m.

Overview: **Sally M. Davis**, Ph.D., Professor of Pediatrics and Director, Prevention Research Center, University of New Mexico, Center for Health Promotion, Albuquerque

10:15 a.m. – 10:25 a.m.

### Participant Dialogue

### Treatment

**Focus of session:** Review the evidence on efficacy of the various treatment modalities. Comment on the relevance of the research, e.g., what has been studied; what are the constraints when generalizing to treatment of the general population or subgroups. Suggest research priorities.

10:25 a.m. – 10:45 a.m.

Overview: **Samuel Klein**, M.D., Director, Center for Human Nutrition, Washington University School of Medicine, St. Louis

10:45 a.m. – 10:55 a.m.

Discussant: **Thomas A. Wadden**, Ph.D., Professor of Psychology and Director, Weight and Eating Disorder Program, University of Pennsylvania, School of Medicine, Philadelphia

10:55 a.m. – 11:05 a.m.

Participant Dialogue

### Practical Applications to Clinical Practice and Community Settings

**Focus of session:** Review the weight reduction/maintenance approaches in clinical practice that have been proven to be efficacious. Describe any barriers and limitations to applying successful interventions used in research settings to clinical practice. Describe what is needed to translate understanding into culturally appropriate interventions that can sustain long-term success.

Discuss promising integrated systems approaches that may help clinicians assist patients to lose and maintain weight.

Suggest types of study designs, including participatory research, that would facilitate more effective, simple, and practical intervention research. Suggest research priorities.

11:05 a.m. – 11:25 a.m.

Clinical Overview: **Robert Kushner**, M.D., Professor of Medicine, The Feinberg School of Medicine of Northwestern University and Medical Director, Wellness Institute, Northwestern Memorial Hospital, Chicago

11:25 p.m. – 11:45 p.m.

Community Overview: **Njeri Karanja**, Ph.D., Senior Investigator, Kaiser Permanente Center for Health Research, Portland

11:45 p.m. – 12:05 p.m.

Integrated Systems Overview: **Nico P. Pronk**, Ph.D., FACS, FAWHP, Vice President, Center for Health Promotion and Research Investigator, HealthPartners Research Foundation Center for Health Promotion, Health Partners, Minneapolis

12:05 p.m. – 12:15 p.m.

### **Participant Dialogue**

12:15 p.m. – 12:35 p.m.

Break

[Lunch Session: Implications of Obesity Research for Future Advances](#)

### **Asthma**

12:35 p.m. – 12:50 p.m.

**Scott Weiss**, M.D., Professor of Medicine, Harvard Medical School, Brigham & Women's Hospital, Boston

12:50 p.m. – 1:00 p.m.

### **Participant Dialogue**

### **Sleep Disorders**

1:00 p.m. – 1:15 p.m.

**Virend K. Somers**, M.D., D.Phil., Professor of Internal Medicine, Mayo Clinic and Foundation, Rochester

1:15 p.m. – 1:25 p.m.

### **Participant Dialogue**

### **Stakeholder Perspectives**

1:25 p.m. – 1:40 p.m.

**Lynn McAfee**, Director, Medical Advocacy, Council on Size and Weight Discrimination

1:40 p.m. – 1:55 p.m.

**Colonel Marina Vernalis**, M.C., U.S.A., D.O., Chief of Cardiology Service and Medical Director, Cardiac Risk Prevention Center, Walter Reed Army Medical Center

1:55 p.m. – 2:05 p.m.

### **Participant Dialogue**

### **Summary and Prioritization of Critical Research Recommendations**

2:05 p.m. – 3:20 p.m.

### **Cochairs and Participants**

### **Closing Remarks From the Cochair**

3:20 p.m. – 3:30 p.m.

**Claude Bouchard**, Ph.D., Executive Director, Pennington Biomedical Research Center, and Director, Human Genomics Laboratory, Baton Rouge

**Shiriki Kumanyika**, Ph.D., M.P.H., Professor of Epidemiology and Associate Dean for Health Promotion and Disease Prevention, University of Pennsylvania School of Medicine, Philadelphia

3:30 p.m.

Meeting Adjourned

<b>α</b>	Alpha	<b>LEP</b>	Leptin Gene
<b>apoB</b>	Apolipoprotein B	<b>LEPR</b>	Leptin Receptor Gene
<b>AgRP</b>	Agouti-Related Peptide	<b>m</b>	Meter
<b>AHA</b>	American Heart Association	<b>MC4R</b>	Melanocortin-4 Receptor
<b>ANS</b>	Autonomic Nervous System	<b>NAASO</b>	North American Association for the Study of Obesity
<b>ATP III</b>	Adult Treatment Panel III	<b>NCEP</b>	National Cholesterol Education Program
<b>BMI</b>	Body Mass Index	<b>NHANES</b>	National Health and Nutrition Examination Survey
<b>β</b>	Beta	<b>NHLBI</b>	National Heart, Lung, and Blood Institute
<b>CARDIA</b>	Coronary Artery Risk Development in Young Adults	<b>NIDDK</b>	National Institute of Diabetes and Digestive and Kidney Diseases
<b>CBPR</b>	Community-Based Participatory Research	<b>NIH</b>	National Institutes of Health
<b>CDC</b>	Centers for Disease Control and Prevention	<b>NPY</b>	Neuropeptide Y
<b>CHD</b>	Coronary Heart Disease	<b>OSA</b>	Obstructive Sleep Apnea
<b>CNS</b>	Central Nervous System	<b>PAI-1</b>	Plasminogen Activator Inhibitor 1
<b>CO<sub>2</sub></b>	Carbon Dioxide	<b>PCSK1</b>	Proprotein Convertase Subtilisin/Kexin Type 1
<b>CPAP</b>	Continuous Positive Airway Pressure	<b>PIPE</b>	Penetration, Implementation, Participation, Effectiveness
<b>CRP</b>	C-Reactive Protein	<b>POMC</b>	Proopiomelanocortin
<b>CVD</b>	Cardiovascular Disease	<b>QTLs</b>	Quantitative Trait Loci
<b>D&amp;E</b>	Demonstration and Education	<b>RAS</b>	Renin/Angiotensin System
<b>DHHS</b>	Department of Health and Human Services	<b>RCTs</b>	Randomized Controlled Trials
<b>DNA</b>	Deoxyribonucleic Acid	<b>4S</b>	Size, Scope, Scalability, Sustainability
<b>DPP</b>	Diabetes Prevention Program	<b>SIMI</b>	Single-Minded ( <i>Drosophila</i> ) Homolog 1
<b>Ectopic</b>	Refers to Deposition in the Wrong Place	<b>SNPs</b>	Single Nucleotide Polymorphisms
<b>FDA</b>	Food and Drug Administration	<b>SNP</b>	Single Nucleotide Polymorphism
<b>HDL</b>	High Density Lipoprotein	<b>SNS</b>	Sympathetic Nervous System
<b>HF</b>	Heart Failure	<b>TNF</b>	Tumor Necrosis Factor
<b>IL-6</b>	Interleukin-6	<b>U.S.</b>	United States
<b>JNC 7</b>	Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure	<b>WHO</b>	World Health Organization
<b>Kcal</b>	Kilocalories		
<b>kg</b>	Kilogram		
<b>LDL</b>	Low Density Lipoprotein		

## For More Information

The NHLBI Health Information Center is a service of the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health. The NHLBI Health Information Center provides information to health professionals, patients, and the public about the treatment, diagnosis, and prevention of heart, lung, and blood diseases and sleep disorders. For more information, contact:

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