AREA OF FOCUS #2

Obesity

Obesity and overweight represent the most common nutritional problem in the United States, affecting more than one-half of the adult population, an estimated 97 million Americans.

Obesity is a major contributor to diabetes, hypertension, heart disease, stroke, osteoarthritis, and certain cancers.

Obesity is more common among minority individuals in the United States. More than 65 percent of African-American and Mexican-American women are overweight as defined by a body mass index (BMI) above 25.

The prevalence of obesity (BMI above 30) in the United States is increasing in all racial and ethnic groups, but it affects minority populations disproportionately. More than 10 percent of non-Hispanic black women ages 40 to 60 are severely obese, with BMIs above 40.

Rates of obesity in children and adolescents increased by 80 percent from 1980 to 1994 in the United States.

Rates of obesity in American Indian children are more than twice as high as in the Nation's population as a whole.

Obesity in childhood is associated with higher cholesterol levels and higher rates of hypertension, type 2 diabetes, and early coronary heart disease.

Currently, there are no approved medications for the treatment of childhood obesity. Low-calorie diets, behavior modification, and exercise are the mainstays of treatment but have had limited success in the past.

Obesity is an important area of research supported by NIDDK, including basic research on appetite, satiety, energy expenditure, and genes that affect body weight as well as clinical research on the means of treating and preventing obesity.

Current Activities

Look Ahead: Action for Health in Diabetes

Background

Numerous studies have demonstrated the beneficial impact of short-term weight loss on risk factors such as dyslipidemia, hyperinsulinemia, hypertension, and elevated plasma glucose. Based on long-term epidemiological evidence of the health hazards of overweight and obesity and on short-term clinical trial evidence, public health policy recommends weight loss for obese individuals (body mass index [BMI] 30 or above) or overweight individuals (BMI 25.0 to 29.9) with one or more additional comorbidities.

Currently in the United States, 40 percent of women and 25 percent of men are attempting to lose weight, using a variety of means. Despite this fact, few studies have examined the health effects of intentional weight loss over a period greater than 1 year and very few beyond 4 years. Moreover, several major observational studies show a significant association between weight loss and mortality that persists even after attempts to correct for confounding factors (e.g., smoking or preexisting illness). However, most of these observational studies are unable to distinguish between voluntary and involuntary weight loss.

The Look AHEAD trial is a multicenter clinical trial to investigate the benefits and risks of interventions designed to sustain weight loss over the long term. The Look AHEAD trial began enrollment in spring 2001. The study will enroll 6,000 overweight patients with type 2 diabetes over a period of 3 years, randomizing them to either standard medical care or intensive lifestyle modification, which may include pharmacological therapy. The long-term health benefits were monitored, with the primary end points being combined cardiovascular deaths (including fatal myocardial infarction and stroke), nonfatal myocardial infarction, and nonfatal stroke.

A Request for Applications (RFA) for Ancillary Studies in Conjunction with Look AHEAD was released on August 2, 2000. This RFA solicited R01 grants to take advantage of the availability of such a well-described and diverse population of obese individuals with type 2 diabetes undergoing long-term weight loss interventions. The National Heart, Lung, and Blood Institute (NHLBI), National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institute of Nursing Research, and National Institute of Dental and Craniofacial Research cosponsor the RFA. Applicants are encouraged to propose studies that investigate health disparities in subpopulations defined by variables such as race/ethnicity, gender, or socioeconomic status.

Research Goals and Scope

The purpose of this initiative was to solicit applications for a range of basic, clinical, and behavioral ancillary research studies consistent with the aims of Look AHEAD. These ancillary studies can enhance investigation of the response of the various participants' characteristics to weight loss interventions, the impact of weight loss interventions on obesity-related comorbid conditions, the relationship of genetic factors to these responses, and the psychosocial correlates or determinants of behavior change. In addition, the Look AHEAD cohort offers the opportunity

for ancillary studies to examine the incidence or progression of obesity-related pathological conditions, in populations in which additional study is needed, to identify biomarkers for disease risk and to investigate relatively rare or understudied obesity-related conditions in this large sample.

Examples of research topics considered responsive to this RFA include, but are not limited to, the following:

- Genetic Studies, such as mutation and polymorphism detection and genotype/phenotype association studies
- Metabolic/Physiological Studies, such as substrate use as a function of treatment or weight loss, lipid metabolism and kinetics, insulin action and glucose disposal, the modulation of inflammatory markers and mediators, left ventricular mass or function, and the effects of hormonal status on the response to intervention
- Natural History of Co-Morbid Conditions or Impact of Interventions on Conditions, such as sleep apnea, diabetic eye disease, urologic and renal disease, nonalcoholic steatohepatitis, osteoporosis/bone density, osteoarthritis, periodontal disease, and subclinical cardiovascular disease measures
- Psychosocial, Behavioral, and Economic Correlates or Predictors in research areas, such as health and/or physiological outcomes, long-term weight maintenance, eating behaviors, psychopathology, diet and physical activity, and changes and adherence to medications
- Measures and Methodology Studies, such as body composition measures other than total fat and fat-free mass, objective measures of diet or physical activity complementary to those proposed for the Study of Health Outcomes of Weight Loss, measures of subclinical disease, and measures of medication adherence.

Performance Measure

The performance measure will be the number of participants screened and randomized.

Outcome Measure

The outcome measure will be the level of success in the alteration of clinical practice regarding prevention and treatment of obesity and type 2 diabetes.

Environmental Approaches to the Prevention of Obesity

Background

Obesity is the most common nutritional disorder in the United States, and its prevalence is increasing in both children and adults. Minority populations, particularly African-American, Hispanic, and Native American women, are disproportionately affected. Although genetic factors are believed to contribute substantially to a predisposition toward obesity, environmental factors play an important role. The dramatic increase in obesity prevalence over the past two decades is believed to be a consequence of environmental factors that favor increased energy intake along with decreased energy expenditure. It has been suggested that while genetic factors may account for a significant proportion of within-population variability in body weight, environmental factors may account for most variability in body weight between populations or over time. Genetic approaches will undoubtedly provide important insights into the control of body weight, which may eventually lead to improved efforts in prevention and treatment. However, it is unlikely that addressing genetic factors alone will overcome the substantial environmental pressures for overconsumption and sedentary behavior that currently affect Americans.

Environmental factors believed to play a role in the development of obesity include those that increase energy intake, such as advertisements for and the low price of high-energy density foods, the consumption

of larger portion sizes, greater frequency of restaurant meals, and the use of more fast foods and convenience foods. For infants, bottle-feeding may also increase energy intake relative to breastfeeding. Numerous environmental factors also lead to decreased energy expenditure. Work is more likely to be sedentary than in the past, with near universal use of automated equipment and electronic communications. At home, wireless phones, remote controls, and various labor-saving devices for household chores also decrease physical activity. More time is spent using the computer, watching television, and playing video games, particularly among children and adolescents. At the same time, the number of schools requiring daily physical education has declined. Suburban communities often lack sidewalks, and the lack of neighborhood resources makes it difficult to walk even short distances to stores and recreation. Many individuals report difficulties going out to exercise because their neighborhoods are perceived as unsafe. In addition, children in day care or in before-school and afterschool care often lack facilities to engage in, or have adequate supervision for, active play.

Prevention of obesity is frequently attempted through educational approaches aimed at improving knowledge and motivation, with a consequent presumed impact on individual lifestyle choices. Such approaches have been largely ineffective at preventing weight gain. Other prevention strategies have focused on changing individual behaviors related to dieting and physical activity but have limited applicability to large populations. In contrast, environmental and policy approaches attempt to modify the environment in which such choices are made rather than rely on individual will. Policy approaches are environmental interventions that involve establishing social, economic, or legal structures within a formal governmental or nongovernmental organization.

Environmental changes that reinforce factors supporting healthy lifestyles and that reduce barriers to healthy lifestyles may also serve to diminish health

disparities, as barriers may be more prevalent in disadvantaged and ethnic minority communities. Approaches that modify the environment to promote healthful eating, increase physical activity, and decrease sedentary behaviors offer the potential for safe and effective programs for obesity prevention that could be widely disseminated. The NIDDK will invite applications to study promising interventions that would target environmental factors that contribute to inappropriate weight gain in children, adolescents, and adults. Investigators should collaborate with organizations and institutions, such as schools, supermarkets, restaurants, religious organizations, recreational facilities, industrial facilities, governmental or community groups, and worksites, to develop approaches that, if successful, could potentially be translated into large-scale interventions.

The need for an obesity prevention initiative has been recognized by a number of NIH advisory groups. In 1994 the National Task Force on Prevention and Treatment of Obesity developed a long-range plan focused on the prevention of obesity and recently reaffirmed obesity prevention as a priority area for clinical research. The recently issued NHLBI/NIDDK *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults* includes a discussion of the

importance of preventing obesity and suggestions for strategies to be attempted. This review includes recommendations for research on obesity prevention. The February 1998 NHLBI *Report of the Task Force on Behavioral Research in Cardiovascular, Lung, and Blood Health and Disease* also recommended the development of obesity prevention research efforts. In December 2000, the Surgeon General held a listening session in an effort to develop a national action plan to combat overweight and obesity. The session identified obesity prevention as a critical target and suggested that efforts focus on environmental factors, including the family and community, schools, worksites, the health care delivery system, and the media.

Research Goals and Scope

This RFA responds to the need for systematic studies of environmental approaches to the prevention of obesity. Although many environmental factors have been cited as contributing to obesity, there have been few controlled studies showing that changes in these environmental factors will prevent weight gain. The sponsoring organizations will encourage the submission of grants for innovative studies, with a goal of modifying the individual, family, group, or community environment such that inappropriate weight gain is prevented by improvements in diet, increases in physical activity, and/or decreases in sedentary behaviors. For purposes of this RFA, prevention of obesity includes the primary prevention of overweight and/or obesity, prevention of additional weight gain or increase in body fat in those already overweight and/or obese, and prevention of weight regain following weight loss. However, studies of weight management programs or the use of medications or dietary supplements to prevent weight gain are not appropriate. Applications should address the content of the intervention (e.g., relative focus on aspects of diet, physical activity, sedentary behaviors, combinations of these, other factors), the setting of the intervention (e.g., in health care settings, community groups, recreational facilities, home, school), and the method of intervention delivery (e.g., individual, family, group, community). Applications targeting groups or populations at high risk for the development of obesity will be encouraged.

Performance Measures

The performance measures will include the number of grants funded, the quality of proposals, and the level of funding.

Outcome Measures

The outcome measures will include the successful modification of the environment to promote healthful eating, increased physical activity, decreased sedentary behaviors, and the potential for safe and effective programs for obesity prevention.

Pathophysiologic Mechanisms of Obesity-Associated Cardiovascular Disease

Background

The adult U.S. population, whose prevalence of overweight and obesity now exceeds 50 percent, is experiencing a mass exposure to obesity-related cardiovascular risk factors and will suffer the inevitable clinical consequences in years to come. Also alarming are the ever-rising rates of overweight and obesity in children and adolescents. The increased rates of non-insulin-dependent diabetes mellitus (type 2 diabetes) and the evidence of increased risk of hepatic damage in overweight adolescents make it clear that children are not protected from the metabolic perturbations that accompany excess adipose tissue stores; we do not know what the consequences might be for a still-developing cardiovascular system if obesity is present during growth and maturation.

Overweight or obese individuals experience greatly elevated morbidity and mortality from nearly all the common cardiovascular diseases (CVDs)—stroke,

coronary heart disease, congestive heart failure, cardiomyopathy, and possibly arrhythmia/sudden death. This is partly attributable to comorbidities (e.g., type 2 diabetes, insulin resistance, hypertension, dyslipidemias, sleep apnea). The residual independent effects of obesity on cardiovascular risk, however, also suggest a role for less well-characterized mediators, such as sleep-disordered breathing and other causes of chronic sleep loss. Because the primary treatment and prevention of obesity often fail or are only partially successful, there will be increasing demands to treat the cardiovascular conditions attributable to obesity. To develop rational therapeutic approaches, it is necessary to understand the basic biology of obesity-related CVD.

Emphasis will be placed on linking the current knowledge of adipocyte and adipose tissue metabolism and function with cardiac and vascular biology or sleep regulation. Major areas needing further research and clarification include (1) the role of adipose tissue as a proinflammatory secretory organ affecting multiple components of the cardiovascular system (e.g., blood pressure, lipid metabolism, vascular reactivity, myocardial metabolism, clotting and inflammatory pathways) at every level of biological organization; (2) lipid infiltration (i.e., lipotoxicity) as a novel pathophysiologic mechanism; (3) cardiovascular, respiratory, and sleep neurobiology during obesity; (4) the impact of excessive adipose tissue burden on the final maturation of the cardiovascular system in young animals; (5) the specific pathophysiology of obesity cardiomyopathy; and (6) the complex interactions between chronic sleep loss, hypertension, insulin resistance, and other endocrine dysregulation syndromes.

In addition, important knowledge gaps continue to exist for many "classical" risk factors. For example, the exact mechanism by which hyperinsulinemia contributes to CVD is not well understood, but it cannot simply be explained by an association between insulin resistance and other known risk factors (e.g., dyslipidemia). Innovative approaches to understanding the molecular mechanisms by which insulin resistance and hyperinsulinemia cause endothelial dysfunction will contribute to understanding the pathophysiology of obesity-associated CVD.

The purpose of this initiative is to stimulate new research approaches to clarify the biological basis of various obesity-related CVDs, including atherosclerosis, cardiomyopathies, heart failure, arrhythmia/sudden death, and sleep-disordered breathing (sleep apnea). Funds would support basic and clinical mechanistic studies and the development of needed research resources.

Research Goals and Scope

Novel experimental approaches taking advantage of the cardiovascular and respiratory dimensions of genetic and experimental models of obesity would be encouraged. New animal models are needed, including immature and growing animals. Distinct lean and obese phenotypes, and other well-defined intermediate phenotypes, in humans and large animals also may have high utility for mechanistic studies. In addition, new methodologies, such as microarray technology and targeted gene expression, may help speed the search for markers that predict disease, track its development, or influence treatment outcomes.

The budget for this program is structured to provide funds primarily for regular research project grants. In addition, it is envisioned that several projects could encompass the development of resources needed to advance the field; these resources would be supported with the provision that they be made readily available to other researchers. The costs for such approved research resource components would be provided on a scale up to that of the main project.

Performance Measures

The performance measures will include the number of grants, the quality of proposals, and the funding level of this initiative.

Outcome Measures

The outcome measures will include the number and quality of publications resulting from the studies and the successful development of new diagnostic, preventive, and therapeutic measures.