Obesity Workshop III

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Toward a New Conceptualization of Treatment and Prevention of Obesity

Obesity is a prevalent, serious, and refractory public health problem. Recent long-term results from treatment studies have shown discouraging rates of relapse. These findings, combined with a growing antidieting movement, have called into question whether weight loss is possible with current methods and whether obesity should be treated at all.

An important issue in this debate is whether efforts to lose weight can be successful. A frequently cited statistic, that 95% of overweight persons regain lost weight, is based on surprisingly weak data. What little is known about long-term results comes entirely from specialty research clinics, where subjects are heavier, display more psychopathology, and are more likely to be binge eaters than overweight people in general. These are negative prognostic factors, so extrapolating these subjects’ results to people who lose weight by any method may be a serious mistake. Research is clearly needed to test the effectiveness of weight loss efforts of all types.

Even if sustained weight loss occurs more often than expected, there is a desperate need to improve treatments for obesity.1-3 A “conceptual house-cleaning” is in order and bold, innovative perspectives are needed. One means of advancing conceptually is to place past, current, and future research into a generational model. To propose such a model, four generations of research may be considered.

The first generation of treatment studies on obesity consisted of atheoretical research with small samples, minor weight loss, short follow-up periods, and controlled studies in which the challenge was to find a single best treatment. The second generation spanned the mid-1970s through the mid-1980s, and although weight losses were more impressive and follow-up periods longer, relapse appeared nearly universal if subjects were followed up for long enough, and the search continued for a best treatment. We are now early in a third generation of research. There is some recognition of heterogeneity in the obese population, especially now that binge eating has been identified as a problem requiring special treatment. Theory is playing a more prominent role, and there is more attention to targeted populations (eg, diabetics and binge eaters).

This paper argues for a fourth generation of research to begin immediately. This generation would involve a strong connection with theory, integration with basic research, increased focus on smaller but better-maintained weight losses, greater emphasis on heterogeneity, more research on weight maintenance, and, above all, an effort to match individual patients to treatments.

To successfully undertake this fourth generation of research, we must consider specific questions to be priorities:

1. Who should lose weight?
2. Who can lose weight?
3. How much can be lost?
4. What is the best approach for an individual?
5. How can weight maintenance be enhanced?

With any problem as resistant to treatment as obesity, the prospect of prevention is appealing. The likely targets of prevention efforts, according to most discussions, would be children with early signs of excess weight gain and children of overweight parents. However, these may be the very people with a genetic tendency to gain weight, and interrupting this process may create serious problems. Animal research suggests that such individuals may preserve body fat at the expense of lean body mass, even if weight is reduced. Increased problems with body image disturbances and eating disorders would be expected if children become the focus of even more concern about weight and dieting, particularly if their biology creates strong opposition to efforts to lower weight. Therefore, discussion of prevention should be undertaken with careful consideration of methods for intervention and appropriate target groups.

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Obesity is recognized as an important risk factor for cardiovascular disease.4,5 However, the means by which it interacts with or amplifies the effects of other risk factors needs further study.6 Nevertheless, the prevalence of obesity and progression toward a more obese state by many Americans underscore the need to develop better strategies for behavior change to prevent excess weight gain and improve adherence to obesity treatment.7

Four broad areas of influences on obesity or its treatment were discussed by the working group: (1)
regulated or internal biological factors (genetics, metabolism, and nutrient needs), (2) naturally occurring or imposed behavioral factors (diet, exercise, drugs, and surgery), (3) integrated biological and behavioral factors (psychology, eating patterns, and weight goals), and (4) lessons from animal models (complex etiologies). Research priorities and recommendations for educational programs and public policies were derived from these discussions.

**Regulated or Internal Biological Factors**

**Genetics**

During the past decade much progress has been made in the understanding of the genetic bases of the various human obesity phenotypes. Obesity aggregates in families, but familial resemblance is caused not only by genetic effects but also by lifestyle, environmental, and cultural factors. Thus, the genetic heritability of the obesity phenotypes accounts for 50% or less of the age- and gender-adjusted variances. There is growing acceptance of the notion that the effects of single segregating genes on such complex phenotypes can be identified if the experimental conditions are right, and that the DNA mutations associated with human obesities will eventually be discovered. Data generated by association and linkage studies, quantitative trait loci and positional cloning research strategies, and transgenic mouse models are all sufficiently promising to suggest that these aims can be achieved. However, there are many difficulties to overcome. For instance, most human studies are based on poor assessment of phenotypes and are strikingly deficient in intermediate phenotype data. Moreover, the major determinants of human energy balance (energy intake, dietary fat intake, resting metabolic rate, thermic response to food, level of habitual physical activity, and nutrient partitioning) are all of rather low heritability and vary considerably from day to day as well as over the years in any given person.

Technological advances have made it possible to define the genetic and molecular bases of human obesity. Networking between various laboratories with complementary expertise would greatly enhance the necessary research programs. Research would also greatly benefit from the development of large familial data bases (preferably over three generations), establishment of lymphoblastoid cell lines, and proper measurement of the various obesity phenotypes and of an extensive panel of intermediate phenotypes. Regardless of inherited susceptibility to obesity, prevention and early treatment for those at risk should remain a priority.

**Metabolism**

The endocrine system is critical in translating lifestyle factors such as overnutrition and underactivity into the excess adiposity associated with obesity. In the obese patient, changes in hormone secretion and action result from both the effects of ongoing positive energy balance and excess adiposity. In developing new treatments for obesity, it is important to remember that there are several human obesity defined by differences in fat distribution, hormonal profiles, and metabolism. It is clear that changes in endocrine function can affect both the pathogenesis and treatment of obesity. Abnormalities in insulin secretion and action are central to many of the observed metabolic changes in the obese patient and may play a role in the etiology and maintenance of the obese state. Similarly, reproductive hormonal abnormalities appear to be closely related to obesity and may also have special significance for obesity in women throughout the various stages of development and during pregnancy. The adrenal gland axis, including the secretion of corticotropin-releasing factor in the central nervous system, may be important in mediating the increased food intake associated with depression, stress, and high levels of glucocorticoids. An understanding of the role of the endocrine system is important to strategies for both treatment and prevention of obesity in the population and in individual patients. In addition, future research should be done on individual factors such as age, gender, and degree of adiposity as well as on the variability of response to dietary therapy.

**Nutrient Needs**

The present evidence is that to maximize cardiovascular risk reduction, weight management should best be considered a continuum involving both a hypocaloric phase with loss of body fat and a longer-term maintenance plan for keeping weight at healthier levels. Both the weight loss and long-term weight maintenance phases require attention to nutrient needs as well as to establishing healthy long-term eating patterns. Nutrient recommendations for the weight-loss phase fit well with cardiovascular risk reduction strategies, but vary somewhat depending on the energy level provided. The percentage of calories from protein is highest (1.5 g/kg per day) on regimens of less than 600 kcal, moderate (1 to 1.5 g/kg per day) on regimens of 600 to 1199 kcal, and lowest (0.8 to 1.5 g/kg per day) on regimens of more than 1200 kcal. Generally, 30% of total energy from fat is recommended. When weight-loss regimens limit intake to less than 1200 kcal, multivitamin and multimineral supplementation is usually required. Electrolyte intakes are kept relatively low with a minimum of 500 mg sodium and 2000 mg potassium.

Ideally, the weight maintenance phase recommendations are for intakes conforming to the general pattern of the National Cholesterol Education Program guidelines, and fiber intakes of 20 to 30 g/day are suggested. Unfortunately, many popular weight-reduction diets fail to conform to such recommendations, and some impose considerable nutritional or health risks as well as economic and psychological costs. Popular diets and weight-loss programs can be considered in terms of 10 essential criteria (the “10 Cs”) to evaluate whether they are likely to contribute to healthy weight control. The 10 Cs are calories, composition, costs, consumer friendliness, ability to cope with existing health problems, incorporation of components of sound weight management (healthful hypocaloric or maintenance diet, physical activity and exercise, and behavior modification), continuation provisions for long-term maintenance of healthy weights, incorporation of chronic degenerative disease risk reduction, inclusion of a context of risk reduction in all behaviors, and consistency with nutrition and health science.

Future research on long-term behavior change and health should address how people interpret recommen-
dations and choose their diets to attain "healthy" and "desirable/ideal" weights. In addition, better understanding of the long-term consequences of fad diets and of how nutrient needs are met should help us target food choices and eating patterns. Finally, practice standards for treatment of the different obesity complications by various risk factors should be established and validated.

Natural or Imposed Behavioral Factors

Diets and Foods

Although dietary compliance is a complex subject, a better understanding of specific dietary components that either increase or decrease the likelihood of compliance will help in planning more effective diets for weight loss and long-term weight maintenance. Several studies have identified difficult and easy dietary modifications by men and women who have participated in nutrition intervention programs designed to reduce fat intake. In the Women's Health Trial and the Multiple Risk Factor Intervention Trial, decreased intake of high-fat meats and desserts were difficult changes for participants. Decreased use of fat as a flavoring and decreased consumption of sauces were difficult for women, and decreased consumption of high-fat cheese and of high-fat snacks were difficult for men. In contrast, increased intake of fat-modified foods and changes in food-preparation methods were easy for subjects in both studies. In another study, computer modeling techniques were used to identify a variety of dietary fat-reduction strategies for typical menus for men and women. The strategies were typified by decreased intake of fat-containing foods by modification, substitution, and reduction. For men, a single dietary strategy (use of lean meat) was effective, but for women a combination of strategies was necessary. These theoretical dietary fat-reduction strategies reduced energy intake by 150 to 400 kcal. These findings suggest that the numerous fat-modified products on the market may facilitate adherence to contemporary dietary recommendations, although there is no information about the actual, specific food behavior responses of obese or overweight people. The effect of these new products on the incidence of obesity and overweight in the United States remains to be established. Future research should further examine the role of total fat and specific fatty acids in the diet, especially as new foods appear on the market. Furthermore, comparisons should be made between simple messages about specific food choices (particularly about fat) and complex messages about the total diet and overall effects on short- and longer-term compliance and on specific individuals and groups.

Exercise or Activity

In highly industrialized countries sustained exercise while working or traveling has diminished. This trend has been accompanied by a per capita reduction in energy intake, but not one large enough to match the reduction in energy expenditure. Therefore, in a sizeable proportion of the population there is a moderate energy excess, resulting in a slow but inexorable accumulation of body fat as the years pass. Because it is unlikely that physically demanding jobs will ever again become widespread, there are three major approaches to the prevention and treatment of obesity: (1) further reduce daily energy intake, (2) increase off-the-job physical activity, and (3) adopt some combination of the above. Permanent reduction in daily energy intake on the order of 50 to 200 kcal is likely to help with weight maintenance after weight loss has been achieved. Increased off-the-job exercise (eg, in leisure time and while going to and from work) without restriction of energy intake may result in some gradual loss of body fat, or at least may prevent or slow weight gain over time. Substantial fat loss at the end of 1 year has been demonstrated in men who jogged but whose energy intake remained stable over this time. In a 2-year study of men in a jogging program, slow, progressive loss of body fat occurred despite modestly increased energy intake. Several studies have also shown that addition of an exercise component to a fat- and energy-reduced diet increases the rate of body fat loss substantially with minimal loss of nonfat body mass. For weight maintenance, the combination of regular exercise and continued adherence to the prudent diet seems promising. Long-term (5-year) studies are still needed, along with research to establish which forms of increased physical activity are most acceptable or feasible for various overweight and normal-weight, free-living, sedentary populations.

Drugs and Surgery

Recent studies suggest that drugs may have a role in long-term obesity treatment, and for selected patients surgery is highly effective. Both of these treatments produce the alterations in behavior that are the goal of standard behavioral therapy. Specifically, all types of obesity-treatment surgery and most obesity-treatment drugs reduce food intake, at least initially, and some drugs and some types of surgery appear to increase energy expenditure.

Weintraub et al demonstrated that fenfluramine and phentermine produced and maintained moderate weight losses for 3 1/2 years in some subjects. When they stopped taking the drugs, the subjects regained weight. Phentermine, a centrally active adrenergic-stimulating agent, suppresses appetite and may increase energy expenditure modestly. Fenfluramine, a centrally acting serotonin agonist, increases serotonin release and has some activity in preventing serotonin reuptake by central nervous system neurons. In a European multicenter trial, about 10% of obese subjects taking fenfluramine maintained a loss of more than 20% of initial body weight after 1 year, compared with only 5% of subjects taking a placebo. More than 25% of subjects taking phenoxypropanolamine had a 12-week weight loss of 5 kg, compared with only 2% of subjects taking a placebo (P < .001). These data and the large variations in weight loss of individuals taking obesity-treatment drugs support the hypotheses that specific biochemical defects are responsible for subtypes of obesity and that different drugs may correct these defects. Research is needed to identify predictors of response to a given obesity-treatment drug and the mechanisms of these drugs' action.

Obesity-treatment surgery produces degrees of weight loss that are almost never achieved with behavioral or medical therapy, but the mechanisms of action are poorly understood. Jejunoileal bypass surgery pro-
duces an initial dramatic reduction in food intake and body weight. Food intake returns toward baseline, but weight loss is maintained, and malabsorption plays only a minor role.\textsuperscript{25,26} Animal studies demonstrate that jejunileal bypass surgery increases energy expenditure. Exposure of the lower ileum to nutrients appears to be responsible for the changes in weight and food intake.\textsuperscript{26} Because of the high incidence of side effects, Jejunileal bypass surgery has been replaced by vertical banded gastroplasty and gastric bypass surgery. Vertical banded gastroplasty is simple to perform and has fewer perioperative complications than gastric bypass surgery but produces a lesser long-term weight loss.\textsuperscript{27} The mechanism of weight loss with vertical banded gastroplasty appears to be the mechanical barrier to food intake that is created. Weight loss with gastric bypass surgery is associated with dumping syndrome, a rapid transit of nutrients into the small intestine. Research is needed to identify the mechanisms of action of gastric bypass surgery.

**Integrated Biological and Behavioral Factors**

**Psychological Correlates**

Most weight-loss treatments result in only temporary losses, followed by slow regain. Factors positively correlated with the most favorable results in terms of weight loss include self-monitoring, goal-setting, social support, and length of treatment. Maintenance is correlated with regular physical activity, self-monitoring, and continued contact with therapists. Regain is associated with life stress, negative coping style, and emotional or binge eating patterns. The implications of these findings are that people trying to achieve and maintain weight loss should (1) avoid restrictive dieting, (2) focus on avoiding binge eating, (3) set realistic goal weights, (4) focus on health rather than appearance, (5) focus on self-esteem, (6) ensure that they have social support, and (7) emphasize exercise.\textsuperscript{28} Research is needed to clarify how to appropriately match individuals to different treatment approaches and why certain approaches work. For example, the effects of nonrestrictive dieting (gradual shifts in eating style towards lower-fat and lower-energy foods without perceptions of deprivation) on long-term weight management would provide important information about improving compliance. Likewise, research on the development of self-regulated physical activity and exercise habits in the obese as well as in normal-weight people for weight control would prevent initiation or exacerbation of obesity. Finally, opportunities for and emphasis on healthy eating rather than on dieting should be made readily apparent.

**Eating Patterns**

It has been estimated that approximately 30\% of obese patients who seek treatment are binge eaters. Obese binge eaters appear to be a distinct subgroup with identifiable clinical features and particular treatment needs. Binge eating (ie, the uncontrolled consumption in a discrete period of time of an amount of food definitely larger than most people would consume under similar circumstances) has become the focus of basic and applied research in the field of eating disorders. Amid significant controversy, the forthcoming *Diagnostic and Statistical Manual of Mental Disorders-IV* will include the new diagnostic subcategory “binge eating disorder” as an example of “Eating Disorders Not Otherwise Specified.” Compared with nonbingers, obese bingers eat significantly more food in laboratory studies when instructed to binge or eat normally, report a history of greater weight cycling, have more attitudinal disturbance concerning body weight and shape, and show significantly greater levels of associated psychopathology, especially depression.

Preliminary data have yielded promising findings on the pharmacological and psychological treatment of binge eating in obese patients. However, reduction of binge eating has not yet resulted in significant weight loss.\textsuperscript{29} Clearly, etiologic factors, physiological and psychological mechanisms, and behavioral and environmental synergisms need further elucidation. The relations among binge eating, dieting, and obesity need to be established. Future research to assess the presence of binge eaters in studies of obese individuals and to determine the effects of binge eating on the course of and response to treatment will provide needed information for the development of effective treatments to facilitate weight control, health, and psychological functioning.

**Weight Goals**

For many years, the 1959 Metropolitan Life Insurance Company table of desirable weights, based on observations of minimal mortality among insured subjects, served as the primary desirable-weight guideline for Americans. The sex- and height-specific suggested weights corresponded to a body mass index of approximately 21 to 22. The recommended weights were increased slightly in 1979, and in 1990 new guidelines were issued by the US government. The new guidelines suggested substantially higher desirable weights after age 35. The new guidelines were said to have been based on the National Academy of Sciences review, *Diet and Health*, but that document made no such recommendations and, in fact, cautioned against weight gain with age.\textsuperscript{30}

The available literature is limited by at least three general problems: (1) lack of control for confounding variables, particularly smoking and alcoholism, (2) inadequate accounting for the effects of preclinical disease on weight, and (3) overcontrol for physiological variables such as blood pressure and glucose levels, which mediate the adverse effects of obesity. Despite these limitations, the best available evidence supports the validity of the older Metropolitan tables and suggests that the recent guidelines are too high. Given the extreme difficulty of maintaining substantial weight reductions and uncertainty about the benefits, priority should be given to preventing excess body weight and overall weight gains. Thus, weight guidelines might be most appropriately used as boundaries as people go through life, indicating the need for modest behavioral adjustments in eating and activity levels before obesity occurs. The guidelines are probably unrealistic targets for people who are already substantially obese. Ancillary considerations, such as the presence of lipid or blood pressure abnormalities, may add to the motivation for weight stabilization or loss. However, excess weight without these considerations should not be viewed as benign because it is highly predictive of some
of these complications, which are better prevented than treated.

Research priorities include an improved understanding of the health effects (in terms of cardiovascular and overall mortality) of weight loss and weight cycling; description of the health effects of body fat distribution independent of weight and overall adiposity; elucidation of ethnic and gender differences in the relations between fatness and fat distribution and disease incidence; and the definition of practical and achievable weight loss goals for overweight people.

Lessons From Animal Models

The use of animal models, and in particular of rodent models, of obesity allows researchers to examine the etiology of obesity in more detail. All obesities are defined by increased white adipose tissue mass, although molecular, cellular, metabolic, and behavioral characteristics may differ. Three models of rodent obesity (diet-induced obesity, obesity produced by physical inactivity, and genetic obesity) facilitate our studies. Although not all laboratory animals are equally susceptible to diet-induced obesity, this model is highly relevant to humans. Diet-induced obesity in animals may be produced experimentally by a variety of techniques, including increasing energy intake, increasing metabolic energy efficiency by changing the pattern of eating from nibbling to meal feeding, and altering the composition of the diet from low fat to high fat or feeding a diet high in fat and sugar. Rats also become obese when they are allowed to eat a variety of palatable foods. The effect of a high-fat diet depends in part on the type of fat in the diet and the genetic background of the animal. There are also different responses to a high-fat diet within a given strain. Although obese animals are not always less active than normal-weight ones, inactivity is often associated with obesity. Other influences may be the strain and sex of the animals, composition of the diet, and the duration, type, intensity, and frequency of exercise. There is excellent evidence that routine physical activity is a key to weight maintenance in humans and that cessation of activity leads to weight gain. Genetically obese animals, on the other hand, are categorized as to whether the trait is expressed through single-gene dominant, single-gene recessive, or polygenic inheritance. When obesity is fully developed, the different genetic models have similar alterations in metabolic pathways, including hyperphagia, glucose intolerance, blunted brown adipose tissue thermogenesis, increased white adipose tissue mass, hyperplastic and hypertrophic white adipose tissue, pancreatic islet hypertrophy, and impairment of the sympathetic nervous system. Future research advances largely depend on the use of animal models in the study of biomarkers to predict obesity, to better understand the interrelations between obesity and other diseases, and to further define relations between dietary components and energy balance. With the use of genetic models, progress can be made toward the understanding of candidate genes associated with metabolic processes involved in obesity or of the factors regulating these genes. Finally, the development of new models (ie, transgenic) and methods will point us toward isolating new factors, which may be independent of behavioral factors, for the development of targeted therapies (eg, potential drug treatments) to improve overall compliance and weight management goals.

Summary

The workshop provided the opportunity to discuss issues and develop and integrate ideas. The following recommendations for public policies, education programs, and high-priority research initiatives were developed:

Recommendations for Public Policies

- Focus on prevention by requiring school programs to emphasize appropriate diet, physical activity, and general health guidance to promote cardiovascular health and prevent disease through federal funding
    - Provide better access to exercise (city planning, work-site interventions)
    - Influence food availability and accessibility
    - Influence reimbursement policies for effective early intervention and prevention strategies for obesity
    - Reevaluate policies for use of drugs in the treatment of obesity

Recommendations for Education Programs

- Sponsor scientific workshop to
    - Define the most appropriate weight standards for prevention and treatment
    - Identify who should lose weight and why, when, and how
- Promote the fact that obesity is an important health risk factor, even at moderate levels, and that excess visceral fat is particularly hazardous
- Target health care professionals, consumers, and the media for education about
    - Nature of obesity as a heterogeneous syndrome
    - Recommendations for diet, exercise, behavioral interventions, drugs, and surgery
    - Recognition of special needs of populations of different ethnicity, gender, age, etc
    - State-of-the-art treatment and treatment programs

High-Priority Research Initiatives

- Build better bridges between basic research and treatment/prevention practices
- Acknowledge that obesity is a heterogeneous syndrome that may best be characterized as different obesities
    - Research on defining subtypes
    - Implications for etiology and treatment
    - Better characterization of genotypes and phenotypes
- Study the effects of weight loss, weight gain, and weight cycling on medical and psychosocial outcomes and mortality
- Explore the concept of "reasonable" weight and weight loss goals for those who are overweight
    - Define what, for whom, when, and why
    - Specify criteria and establish definitive guidelines
    - Test and validate in clinical studies
    - Define realistic, achievable, maintainable losses
    - Focus on differences between intervention and prevention strategies for people with and without known cardiovascular disease risk factors
• Prevent initiation and exacerbation of obesity
  - Develop behavioral, medical, and psychological targets
  - Consider developing a public health model
  - Examine the role of “small” energy differences induced by physical activity (eg, walking) or diet (eg, specific foods)
  - Understand and prevent weight fluctuations
  - Emphasize weight maintenance

• Develop improved strategies to characterize individuals, subgroups, and special populations to increase adherence to better-defined interventions
  - Match individuals to treatment(s)
  - Develop clinical practice guidelines
  - Better integrate theoretical models into targeted behavior change
  - Explore individual, additive, and interactive effects of diet and exercise
  - Do further research on the use and potential of drugs and surgery with long-term clinical trials

• Use animal models to answer research questions
  - Control of adipocyte proliferation and differentiation
  - Hormonal alterations in obesity (eg, alterations in insulin secretion)
  - Candidate genes associated with obesity

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