

Hypertension

JOURNAL OF THE AMERICAN HEART ASSOCIATION



*Learn and Live*SM

Dietary Therapy for Obesity: An Emperor With No Clothes

Allyn L. Mark

Hypertension 2008;51;1426-1434; originally published online May 12, 2008;

DOI: 10.1161/HYPERTENSIONAHA.106.085944

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214

Copyright © 2008 American Heart Association. All rights reserved. Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://hyper.ahajournals.org/cgi/content/full/51/6/1426>

Subscriptions: Information about subscribing to Hypertension is online at
<http://hyper.ahajournals.org/subscriptions/>

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax: 410-528-8550. E-mail:
journalpermissions@lww.com

Reprints: Information about reprints can be found online at
<http://www.lww.com/reprints>

Dietary Therapy for Obesity: An Emperor With No Clothes

Allyn L. Mark

The prevalence of obesity has increased substantially in the past 3 decades and is projected to increase further in the years ahead. It increases the risk of diabetes mellitus, dyslipidemia, hypertension, cardiovascular disease, sleep apnea, nonalcoholic hepatic steatosis, gallbladder disease, osteoarthritis, and cancer. The prevention and treatment of obesity is, therefore, a leading challenge facing public health and medicine in the 21st century.

Two stereotypes have dominated thinking in public health, medicine, and the media about obesity. The first stereotype is that the recent surge in prevalence of obesity reflects almost entirely environmental and psychological factors and excludes an important contribution of genetic biological factors. The second stereotype is that obesity should and can be treated primarily by diet and behavioral modification. In this review, I challenge these tenets.

I summarize evidence for a strong genetic neurobiological contribution to adiposity and body weight and assert that common human obesity is, like essential hypertension, a complex multifactorial disease where genetic factors promote sensitivity or resistance to obesity in a toxic environment. This concept of a genetic resistance versus sensitivity to obesity helps explain why many people remain thin in a toxic environment whereas others develop profound obesity.

I then discuss evidence that dietary therapy for obesity generally fails to achieve weight loss maintenance. There is mounting indication that the high rate of relapse from weight loss during dietary therapy occurs because of compensatory biological adaptations that promote lack of compliance and effectiveness. Relapse from weight loss during dietary therapy is not caused simply by lack of discipline and will power.

Finally, I briefly discuss the alternatives to dietary and behavioral therapy, namely bariatric surgery and pharmacotherapy.

As a prelude to my critique of dietary therapy, I begin with a discussion of the role of genetic neurobiological factors in obesity.

Contributors to the Increase in Obesity: The Role of Genetic Neurobiological Factors

The surge in the prevalence of obesity in recent decades, during a time when the gene pool has not changed, has led to the view that environmental changes are the overwhelming contributors to the so-called obesity epidemic. The “Big Two” environmental factors, are said to be: (1) Unending overnutrition related to ubiquitous abundance of low cost/high calorie foods and (2) increasingly sedentary occupations and immobilizing technologies including computers, automobiles, television, and elevators that decrease caloric expenditure.¹

The emphasis on a “toxic environment” in the obesity epidemic has overshadowed evidence for a strong genetic neurobiological contribution to adiposity and body mass in humans. Evidence is mounting that these two factors—a toxic environment and genetic influences—are not mutually exclusive contributors to obesity. Instead, genetic factors can promote either sensitivity or resistance to obesity in a toxic environment.

The Discovery of Leptin and the Revolution in the Genetic Neurobiological Regulation of Appetite and Metabolism

The pioneering discovery of leptin in 1994 by Jeffrey Friedman and colleagues revolutionized understanding of neurobiological regulation of appetite and metabolism.² In 1973, Coleman conducted studies using parabiosis of obese (*ob/ob*) mice with diabetes (*db/db*) or wild-type (+/+) mice.³ He concluded that the *ob/ob* mice are unable to produce a satiety factor to regulate their food consumption whereas the *db/db* mice produce a satiety factor, but cannot respond to it. This study remained mysterious for 21 years until Friedman and colleagues discovered the *ob* or leptin gene and demonstrated that *ob/ob* mice which display increased food intake and severe early obesity have leptin deficiency from mutations in the leptin gene.² Shortly thereafter, it was discovered that *db/db* mice which also display increased food intake and severe obesity have leptin resistance from

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

From the Carver College of Medicine, Center on Functional Genomics of Hypertension, and Department of Internal Medicine, University of Iowa, Iowa City.

Correspondence to Allyn L. Mark, Carver Professor of Medicine, Carver College of Medicine, Center on Functional Genomics of Hypertension, 3111F MERF, University of Iowa, Iowa City, IA 52242-1101. E-mail Allyn-Mark@uiowa.edu

(*Hypertension*. 2008;51:1426-1434).

© 2008 American Heart Association, Inc.

Hypertension is available at <http://hyper.ahajournals.org>

DOI: 10.1161/HYPERTENSIONAHA.106.085944

mutations in the leptin receptor.⁴ Leptin decreases food intake and adiposity and increases energy expenditure in the *ob/ob* but not the *db/db* mice.⁵ These seminal discoveries demonstrated dramatically that appetite and metabolism are tightly controlled by genetic neuroendocrine factors and that adipose tissue is “alive” and acts as an endocrine organ regulating appetite, metabolism, and adiposity. Since then, there has been mushrooming evidence for new genetic neurobiological pathways regulating appetite, metabolism, and adiposity. This evidence has derived largely from studies of mutant or genetically engineered mouse models, but there have also been impressive discoveries in humans.

Monogenic Human Obesity

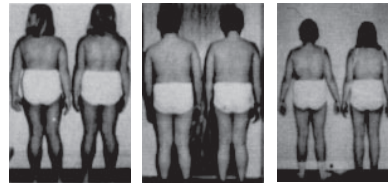
There are rare or infrequent Mendelian human counterparts of both the *ob/ob* mice with mutations in the leptin gene and leptin deficiency⁶ and the *db/db* mice with mutations in the leptin receptor and profound leptin resistance.⁷ Humans with these mutations have voracious appetite, profound early childhood obesity, and other phenotypic abnormalities.^{6–9} In the children with leptin deficiency, treatment with leptin rapidly and dramatically reduces food intake and leads to normal body weight.⁹

A number of other genes have been linked to severe human obesity.^{10–12} Pathogenetic mutations in the melanocortin-4 receptor gene have been identified in 5% of children with severe early onset obesity,¹⁰ and 3% of children with severe early onset obesity have mutations in the leptin receptor.⁸ Thus, monogenic forms of human obesity may represent more than 8% of children with early severe obesity, but it is virtually certain that most human obesity is not monogenic. Instead, as with human essential hypertension, most human obesity is a complex multifactorial polygenic disease involving the interaction of susceptibility genes/alleles and environmental stress.

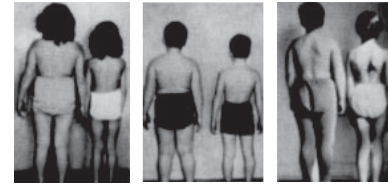
Adoption and Twin Studies

Studies of adopted children and twins support a contribution of genetic factors to regulation of adiposity and body mass under physiological conditions. Stunkard et al¹³ demonstrated that the body mass index (BMI) of adopted children correlates with that of their biological parents (with whom they do not share a common environment) and not with that of their adopted parents (with whom they do share a common environment). In addition, studies of monozygotic twins^{14,15} reveal a high intrapair correlation in BMI with a lower intrapair correlation in dizygotic twins (Figure 1). There are other remarkable features of adiposity and body mass in monozygotic twins. The intrapair correlation in BMI pertains whether the twins are reared apart or together.^{16,17} The intrapair concordance persists over many years.¹⁵ With controlled overfeeding, there is intrapair concordance not only in weight gain but in the pattern of regional fat distribution.¹⁸ These studies demonstrate a strong genetic contribution to the regulation of adiposity and body mass in humans. Indeed, the estimates of heritability of body mass are as high or higher than those for height and arterial pressure where a large genetic contribution is widely recognized. Body mass is a highly heritable human trait.¹²

Body Mass in Twins



Monozygotic Twins (Intrapair Correlation = 0.66)



Dizygotic Twins (Intrapair Correlation = 0.26)

Figure 1. Photographs from Borjeson¹⁴ that portray the strong intrapair correlation in body mass in monozygotic or identical twins and a much lower intrapair correlation in dizygotic twins. The intrapair correlation in body mass in monozygotic twins pertains whether the twins are raised apart or together,^{16,17} and it persists over years¹⁵ and in response to controlled overfeeding.¹⁸ These twin studies indicate a strong genetic influence on body mass and adiposity in humans.

The Concept of Genetic Sensitivity Versus Resistance to Obesity in a Toxic Environment

Despite this evidence from adopted children and twins, many would still ask “how can genetic neurobiological factors contribute to the surge in common human obesity in recent decades since the gene pool has not changed during this time?” This question prompts a discussion of (1) susceptibility genes/alleles; (2) the concept of obesity sensitivity and resistance in animals and humans; and (3) the interaction of genetic and environmental factors in complex multifactorial diseases.

In the absence of environmental stress, susceptibility alleles (as opposed to disease-causing mutations) in genes will not produce a disease phenotype (Figure 2). It is only in the presence of a “toxic” environment that genetic susceptibility will be expressed as the disease phenotype, eg, hypertension or obesity (Figure 2). Thus, the finding that a disease such as obesity increases in frequency and severity in the presence of a “toxic” environment does not exclude an important contribution of genetic factors to the disease. The contribution of susceptibility genes/alleles to obesity has been shown in humans and experimental animals.

There are both rat and mouse models that display striking genetic sensitivity or resistance to obesity when fed high-fat diet. Two rat models merit emphasis—obesity prone and resistant Sprague-Dawley rats developed and characterized extensively by Levin et al^{19–21} and obesity prone and resistant Wistar rats developed by Hill et al^{22,23} and recently studied extensively by MacLean et al.^{24,25}

In humans, both epidemiological and experimental studies support the concept that there are individuals with striking differences in sensitivity versus resistance to obesity. Morbid obesity is increasing at a much faster rate than moderate obesity in the United States.²⁶ There has been a disproportionate increase in the number of severely obese people in

Interaction of Environmental and Genetic Variance in Multifactorial Diseases

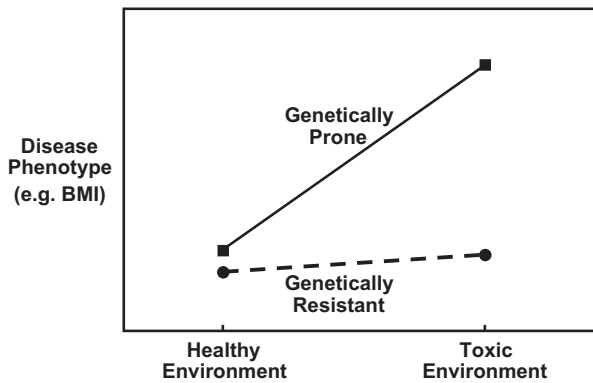


Figure 2. A schematic diagram illustrating the interaction of environmental and genetic variance in complex multifactorial polygenic diseases involving the interaction of susceptibility genes/alleles and toxic environmental factors. Animals and humans with susceptibility genes that render them prone to a multifactorial disease will not manifest the disease phenotype, such as obesity, in a healthy environment. It is only in the presence of a toxic environment that genetic susceptibility will be expressed as the disease phenotype. In a toxic environment, the disease phenotype will emerge in the genetically prone animals or humans, but not in the genetically resistant population. An increase in the frequency or prevalence of a disease phenotype in a toxic environment does not exclude a strong genetic influence on the emergence of the phenotype.

recent years. In contrast, the BMI of adults in the lowest percentiles has not changed nearly as much as the BMI of those in the highest percentiles.²⁷ These observations should be obvious to anyone who has walked the streets of the USA in the past 25 years. These epidemiological data strongly suggest that there are humans who are susceptible to obesity in a toxic environment and others who are relatively resistant.

There is also experimental evidence for the concept of obesity sensitivity and resistance in humans. In 16 nonobese young adults overfed by 1000 kcal per day for 8 weeks, Levine et al²⁸ observed a 10-fold difference in weight gain ranging from 0.36 kg to 4.23 kg (Figure 3). In earlier studies of 12 pairs of identical twins, Bouchard et al¹⁸ observed that the variability in weight gain during controlled overfeeding was strongly influenced by genetic factors. Weight gain among the 24 individuals overfed by 1000 kcal per day for 12 weeks ranged from 4.3 to 13.3 kg. The strongest predictor of weight gain, particularly in visceral fat, with controlled overfeeding was the amount gained by the subject's identical twin. These studies indicate that the concept of sensitivity versus resistance to obesity in a toxic environment has a substantial genetic underpinning.

In summary, adoption and twin studies provide evidence for a substantial genetic contribution to body mass and adiposity in humans. Mendelian monogenic forms of early childhood obesity provide incontrovertible evidence for powerful genetic neurobiological influences on appetite and adiposity in humans. Finally, there are both epidemiological and experimental data supporting the concept of genetic susceptibility or resistance to diet-induced weight gain in humans. This concept of obesity sensitivity and resistance may explain why some individuals develop profound obesity

The Concept of Obesity Sensitivity vs Resistance: Variability in Fat Gain During Overfeeding in Humans

- 16 nonobese volunteers
- Overfed by 1000 kcal per day x 8 weeks
- Fat gain varied 10 fold from 0.4 kg to 4.2 kg.

Figure 3. A summary of experimental evidence from a study by Levine et al²⁸ in which 16 nonobese volunteers who had controlled overfeeding for 8 weeks displayed a 10 variability in weight gain. This finding supports the concept of obesity sensitivity and resistance during overfeeding in humans. A study of controlled overfeeding in identical twins by Bouchard et al¹⁸ indicated that the strongest predictor of weight gain with overfeeding was the amount gained by the subject's identical twin. This study suggests that genetic factors are major determinants of obesity sensitivity or resistance.¹⁸

in a toxic environment whereas others do not. As Bray has said: "genes load the gun and a permissive or toxic environment pulls the trigger."²⁹

The Concept of Gestational and Perinatal Metabolic Imprinting of Offspring and Epigenetic Mechanisms in Obesity

In addition to susceptibility genes/alleles influencing sensitivity or resistance to obesity, there is evidence for a maternal gestational and perinatal "metabolic imprinting" of the offspring.^{30,31} In humans, this concept has emerged primarily from epidemiological studies,³¹ but it has received strong support from experimental studies in rodents.^{30,32} Maternal obesity and high-fat diet during gestation and lactation promote obesity and insulin resistance in offspring of rats.³⁰

A Notable Feature of This Metabolic Imprinting in Rats Is Its Relationship to the Genotype of the Mother

In rats selectively bred to be either genetically prone or resistant to the development of diet-induced obesity, maternal obesity during gestation leads to increased obesity (metabolic imprinting) only in the offspring of the mothers with a genetic predisposition to obesity.³⁰ Thus, the interaction of genetic sensitivity and a toxic environment in the mother during gestation can stamp the offspring with a lifelong predisposition to obesity.

Epigenetic mechanisms, ie, hereditary changes in gene function/expression that occur without changes in DNA sequence, may be involved in metabolic imprinting.^{32,33} These epigenetic changes in gene expression may be triggered by environmental influences, such as maternal nutrition during gestation. The practical implication is that the resulting changes in gene function and susceptibility to obesity may persist throughout life in the offspring.

In summary, maternal obesity and high-fat diet during gestation and lactation can create a long-term sensitivity to obesity in the offspring. This metabolic imprint is apparently linked to an interaction between the mother's genetic predisposition to obesity and her metabolic environment during gestation and lactation. The gestational influences on long term susceptibility to obesity may be transmitted in part by

epigenetic mechanisms. This maternal metabolic imprinting of the offspring introduces another source of biological predisposition to obesity in a toxic environment. Thus, both susceptibility genes/alleles and metabolic imprinting (epigenetic effects) can create a predisposition or sensitivity to obesity that is enduring and beyond purely cognitive and psychological control.

Dietary Therapy for Obesity: An Emperor With No Clothes

A second stereotype is that obesity should and can be treated primarily by dietary and behavioral therapy. What has led to this stereotype? Until recently, we have lacked understanding of the biology of obesity. This led to the view that the surge in common human obesity is solely a behavioral and environmental problem and should, therefore, be treated by behavioral and dietary therapy.

The antidote to this stereotype is relapse from weight loss during dietary therapy and its biological basis. Over 5 decades, it has been demonstrated repeatedly that dietary therapy fails to achieve weight loss maintenance.^{34–36} Stunkard commented on this in 1958.³⁴ Kramer et al confirmed it in 1989.³⁵ Rosenbaum et al stated in 1997 that “approximately two thirds of persons who lose weight will regain it within one year, and almost all persons who lose weight will regain it within five years.”³⁶ One might argue that weight loss programs have improved and that these reports do not reflect the success of the best current programs. Unfortunately, this is not true. In a meta-analysis reported last year, Dansinger et al³⁷ found that dietary counseling produced only modest weight loss and that even this diminished over time. Wilfey et al recently performed a randomized controlled trial to determine whether “maintenance interventions” augmented the effects of initial weight loss programs in obese children.³⁸ One of two maintenance programs improved short-term efficacy of weight loss treatment in the children, but these effects waned over the next 1 to 2 years. In an editorial commentary, Rhodes and Ludwig³⁹ commented: “. . . the data provided a sobering message—despite a statistically significant effect” in maintaining weight loss “. . . the effects of all interventions diminished over time and even at their peak were small.” In addition, Tsai and Wadden⁴⁰ recently evaluated the effectiveness of commercial behavioral weight loss programs. These programs include trained staff, low-calorie diets, physical activity programs, support groups, and counseling on behavioral modification. Despite these inducements to weight loss, these programs produced meager maintenance of weight loss. Many would suggest that the answer lies in more research to improve compliance and effectiveness of dietary and behavioral therapy. After decades of trying, and given the biological mechanisms that promote loss of compliance with dietary and behavioral therapy, I doubt that this will succeed.

Let me acknowledge—a small percentage of people who lose weight by diet and behavioral modification maintain their weight loss. In 1993, Wing, Hill and colleagues^{41,42} started the National Weight Control Registry (NWCR) to recruit and study a group of people who had succeeded at long-term weight loss maintenance, defined as weight loss of

at least 30 pounds maintained for at least 1 year. In 2006, Hill⁴¹ reported that the 6000 individuals in the NWCR had maintained average weight loss of over 70 pounds for an average of almost 6 years. Among these subjects, 4 behaviors and strategies stood out: (1) eating a moderately low fat, high carbohydrate diet; (2) consistent self-monitoring of body weight, food intake, and physical activity; (3) eating breakfast every day; and (4) very high levels of physical activity equivalent to 60 minutes/d of moderate intensity physical activity.

What can we conclude from the study of people who have successfully maintained weight loss? They are a small minority of people who have lost weight. They are highly self-motivated. The primary strategy of more than 90% of these people who are successful in maintaining weight loss is “a high level of physical activity”, ie, moderate intensity physical activity for about 60 minutes/d.⁴¹

Can we produce and maintain such robust increases in physical activity in people who are not self-motivated? Tate, Wing, et al⁴³ conducted a randomized clinical trial comparing standard behavioral therapy (SBT) with high levels of physical activity plus SBT. For 18 months, individuals assigned to high physical activity had an intensive support program. At the end of the 18 months, those assigned to high physical activity plus SBT were indeed performing higher physical activity, but, 1 year after the support program ended, physical activity had declined and there was no difference in activity and weight loss between the 2 groups. This study demonstrates that in most people there is relapse from adherence to high physical activity just as there is relapse from dietary restriction.

Mechanisms of Relapse From Weight Loss: Psychological

There are 2 possible explanations for failure to maintain weight loss during dietary and behavioral therapy. The first is behavioral or psychological, and the second is biological. The psychological explanation holds that obese people lack the will power and discipline to eat less and exercise more. This view is convenient because it shifts the blame to the patient for our lack of effective treatment, but it lacks evidence. To the contrary, in 1961 Albert Stunkard, a psychiatrist who has made many scholarly contributions to understanding human obesity, and his colleagues examined the concept that obese humans have distinctive personality characteristics that predispose them to obesity. In a systematic comparison of obese and lean men reported, Stunkard and his colleagues reported that “no distinctive personality features were found.”⁴⁴ Nevertheless, obese people continue to be stigmatized as lacking the discipline to prevent and treat obesity. As Friedman stated: “In most circles, the conventional wisdom on obesity’s cause has not changed appreciably from the time of Galen, who clearly held obese individuals responsible for their state. . . . Through the ages obese individuals have been held accountable for their condition.”⁴⁵

Mechanisms for Relapse From Weight Loss: Biological

As a counterpoint to the simplistic notion that relapse from weight loss during dieting has a psychological explanation, there is mounting evidence that “voluntary efforts to reduce

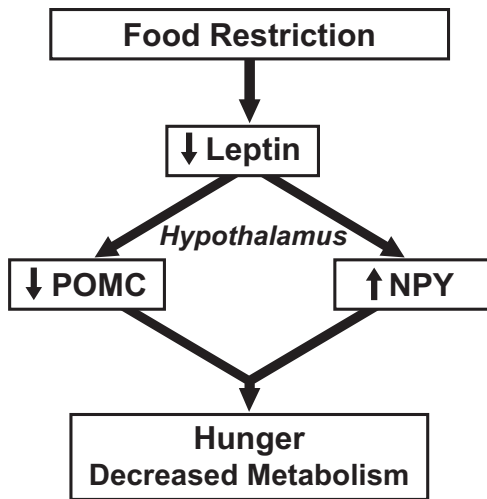


Figure 4. A schematic depiction of changes in leptin and neuropeptides during food restriction.²¹ These compensatory adaptations promote hunger and decrease metabolism. This undermines adherence to low calorie diets and promotes weight regain.

weight are resisted by potent compensatory biological responses.⁴⁵

In obesity prone rats, MacLean et al^{24,25} demonstrated that weight-reduced obese rats manifested a persistent decrease in energy expenditure and an increased drive to eat. As a result, when food became available, the rats displayed an exceptionally high rate of weight regain.^{24,25} Food restriction and weight loss are accompanied by decreases in plasma leptin (Figure 4). This results in decreases in catabolic hypothalamic proopiomelanocortin (POMC) and increases in anabolic hypothalamic neuropeptide Y (NPY)²¹ (Figure 4). These neurochemical changes stimulate food intake and minimize energy expenditure and, thereby, promote weight regain (Figures 4 and 5). As Levin has said, with food restriction and weight loss, “the drive to regain lies mainly in the brain.”²¹

These and other studies in experimental animals provide a contemporary framework for understanding observations made 4 decades ago in obese humans during diet-induced weight loss. Hirsch and colleagues⁴⁶ studied responses to diet-induced weight loss in obese humans in the 1960s. Hirsch later summarized his studies: “my colleagues and I found that patients in their obese state had no specific constellation of behavioral abnormalities or psychological aberrations. Nothing convincingly implicated any psychiatric or psychological disturbance as the cause of their obesity. After these same patients lost weight, however, they mani-

festated many behavioral and physiological alterations. They developed a marked preoccupation with food and dieting, and their physical and mental activity generally slowed down.”⁴⁷

Subsequently, Leibel, Rosenbaum, and Hirsch⁴⁸ demonstrated that weight loss and weight maintenance secondary to a decrease in caloric intake in humans are accompanied by a compensatory decrease in total energy expenditure. This mirrors the changes in energy expenditure in obese rats undergoing dietary restriction and weight loss. This decrease in energy expenditure would protect against starvation during famine, but in an environment prone to obesity it makes maintenance of weight loss difficult (Figure 5).

Dietary adherence declines dramatically within 4 to 12 months and is another major cause of relapse from weight loss during dieting.⁴⁹ Despite claims to the contrary, this occurs with all diet programs including Atkins, Weight Watchers, and Ornish.⁴⁹ Not surprisingly, this decrease in adherence has been attributed to a lack of will power and discipline and blamed on the patients. But there is now incontrovertible evidence for compensatory biological adaptations that increase appetite and undermine adherence to weight reducing diets (Figure 4).

Food restriction and weight loss are accompanied by decreases in leptin (Figure 4). Leptin exerts a potent influence on appetite. Children with congenital leptin deficiency have aggressive food-seeking behavior.⁶ Before leptin treatment, a young child with leptin deficiency consumed in excess of 1100 calories at a single meal, which is approximately half the average daily intake of an adult. With only a few injections of leptin, this was reduced by 84% to 180 calories a day, the typical intake of a normal child.²⁷ Ghrelin, a gastrointestinal hormone that stimulates appetite, might also be involved in loss of dietary adherence during dieting.⁵⁰ Ghrelin normally rises before meals and falls after every meal.⁵⁰ It is increased during diet-induced weight loss, so that with weight-reducing diets, there is more ghrelin stimulating appetite.⁵⁰ Thus, there is mounting evidence that appetite is a tightly regulated biological variable. With dieting and weight loss, there are homeostatic adaptations that stimulate appetite and decrease dietary adherence (Figure 4).

Schwartz et al⁵¹ have reviewed evidence that the homeostatic control system of anabolic (NPY and agouti related peptide) and catabolic (proopiomelanocortin and cocaine-amphetamine-regulated transcript) neuronal pathways regulated by leptin are inherently more vigorous in defending against weight loss than against weight gain.

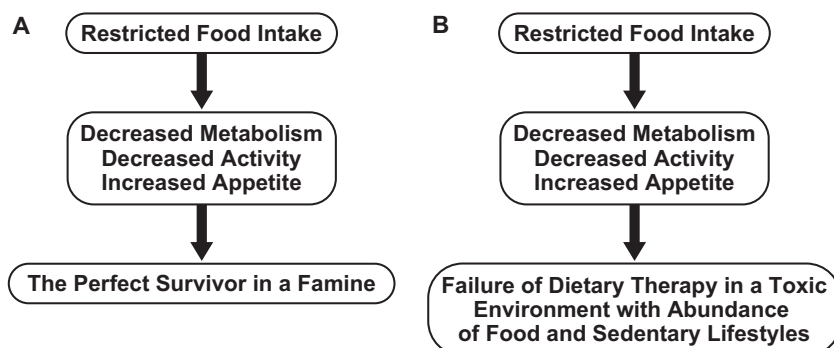


Figure 5. In the midst of famine, the biological adaptations to restricted food intake would protect against starvation and promote survival (A), but in contemporary environments with an abundance of food and increasingly sedentary lifestyles, these biological adaptations make it difficult to sustain weight loss during dietary therapy (B)

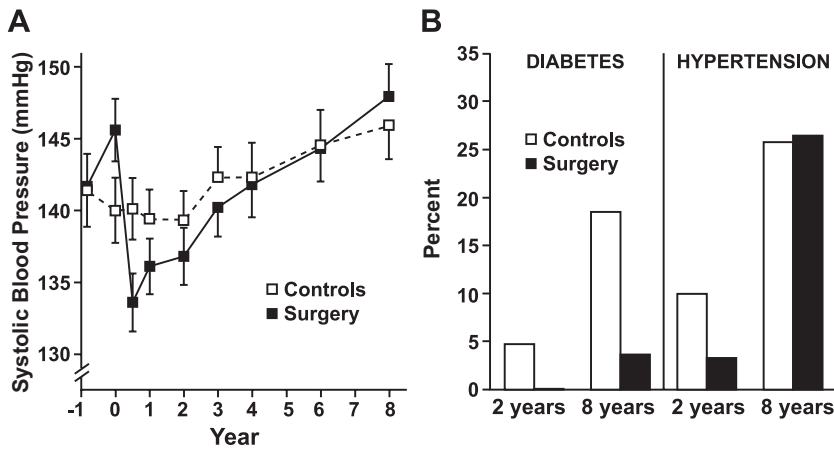


Figure 6. Data from the Swedish Obesity Study^{55,60} showing a differential long-term effect of bariatric surgery on diabetes and hypertension. Blood pressure decreased initially after bariatric surgery, but returned to control levels after 6 to 8 years despite persistent substantial decreases in body weight (left).⁶⁰ In addition, although bariatric surgery was accompanied by a persistent decrease in the incidence and severity of diabetes and dyslipidemia, the 8- to 10-year incidence of hypertension did not differ between the surgical and control groups (right).⁵⁵

In addition, there are nonhomeostatic (reward, cognitive, emotional) cortico-limbic controls that promote ingestive behavior.⁵² In a world of plentiful food, this nonhomeostatic control system has assumed increasing importance in regulating ingestive behavior and may override satiety.⁵² As Berthoud reports, it is simplistic to believe that these nonhomeostatic mechanisms are purely cognitive and can be easily controlled by discipline or will power.⁵² These nonhomeostatic control pathways are under profound neurobiological control.

The Paradox of the Limitations and Dominance of Dietary Therapy

Many leaders in this field have commented on the high rate of relapse from adherence to dietary and behavioral treatment of obesity and its biological basis.^{21,27,29,34,36,47} In an era when we pride ourselves on practicing evidence-based medicine, why then does dietary and behavioral therapy still reign if it is “an emperor with no clothes”? I propose 4 reasons: (1) It is highly profitable for industry and academia; (2) It puts the responsibility for failure on the patient and not the physician; (3) We have not had effective and safe drug treatment for obesity; and (4) In the midst of an “epidemic”, public health officials and physicians are loathe to acknowledge that we do not have effective prevention.

If Not Dietary and Behavioral Therapy, Then What?

If dietary and behavioral therapy is as I suggest “an emperor with no clothes”, then what are the alternatives? It is not my purpose to provide an extensive review of bariatric surgery and drug therapy, but some comments seem necessary.

Bariatric Surgery

Bariatric surgery produces substantial and sustained weight loss in patients with morbid obesity.^{53–58} Other treatments do not.^{53–56} The Swedish Obesity Subjects (SOS) study is the largest prospective (albeit nonrandomized) trial of bariatric surgery.⁵⁵ In 1703 patients followed for 10 years after surgery in the SOS study, there was considerable benefit in lifestyle, diabetes, and dyslipidemia.⁵⁵

Dixon et al⁵⁶ recently evaluated the effects of bariatric surgery (laparoscopic adjustable gastric banding or LAGB) on glycemic control and need for diabetes medications in 60 obese (BMI 30 to 40), type 2 diabetic patients randomized to either surgery or

conventional diabetes, dietary and behavioral therapy. In patients followed for 2 years, the surgical group achieved greater weight loss, glycemic control, and remission of diabetes. One potential caveat of the general applicability of this study is that the magnitude of weight loss with LAGB (20.7% of body weight) was greater than that observed by other investigators.⁵⁹

Surprisingly perhaps, the beneficial effect of bariatric surgery on blood pressure is not as striking. Although a meta-analysis in 2004⁵³ concluded that hypertension resolved or improved in the majority of patients after bariatric surgery, I found it difficult to find the data supporting that conclusion. In addition, the data from the SOS study explicitly challenge the conclusion from the meta-analysis. In the SOS study,⁶⁰ blood pressure decreased initially after bariatric surgery, but returned to control levels after 6 to 8 years despite persistent substantial decreases in body weight (Figure 6). In addition, although bariatric surgery was accompanied by persistent decreases in the incidence and severity of diabetes and dyslipidemia, the 8- to 10-year incidence of hypertension did not differ between the surgical and control groups (Figure 6).⁵⁵ The absence of significant sustained decreases in blood pressure and hypertension despite sustained weight loss after bariatric surgery is perplexing. These data have received little attention.

There have been 2 recent reports that bariatric surgery reduces overall mortality in patients with BMI greater than 34.^{57,58} In the report from the SOS study,⁵⁷ Sjostrom et al compared 2010 patients who underwent bariatric surgery with 2037 matched (but not randomized) control subjects who underwent so-called conventional treatment. The average follow-up was 10.9 years. The investigators concluded that “bariatric surgery for severe obesity is associated with long-term weight loss and decreased overall mortality” and noted fewer deaths from myocardial infarction and cancer in the surgical group.

In the second report,⁵⁸ Adams et al analyzed long-term mortality among 9949 patients who had undergone gastric bypass surgery compared with 9628 severely obese persons identified from applications for driver’s licenses. These investigators concluded that “long-term mortality after gastric bypass surgery was significantly reduced, particularly deaths from diabetes, heart disease, and cancer.” But the rate of death from accidents, poisoning, suicide, and other nondisease causes was higher in the surgical group.

These conclusions regarding bariatric surgery and mortality may be valid, but it is important to note the limitations and caveats of these 2 studies.

First, neither of these studies was a controlled, randomized clinical trial.^{57,58} In neither study was there an attempt to match nonsurgical medical treatment in the surgical versus control groups. This is not a trivial or theoretical concern. In the Adams' study,⁵⁸ the only relevant information about the control group was their cause of death and their weight (self-reported), height, age, and gender when they applied for a driver's license. It is highly likely that the surgical group received better medical follow-up and treatment than the control group. The same concerns apply to the control group in the SOS study.⁵⁷ The SOS study included a prospective matched (but not randomized) control group of patients who elected not to have bariatric surgery. These patients received so-called conventional treatment. Here is the description of the conventional treatment. "Subjects in the control group received the customary nonsurgical treatment for obesity at their center of registration. No attempt was made to standardize the conventional treatment, which ranged from sophisticated lifestyle interventions and behavior modification to no treatment whatsoever."⁵⁷ In neither report was there evidence that cancer surveillance or management of diabetes and cardiovascular risk factors was as good in the control groups as in the surgical groups. All of these factors would introduce bias favoring survival in the patients who underwent bariatric surgery.

Second, in the SOS study,⁵⁷ the cumulative mortality in the surgical and control groups did not diverge until 8 to 10 years after surgery. And in the report by Adams et al,⁵⁸ the only notable reduction in mortality after gastric bypass was seen in patients with extreme morbid obesity (BMI greater than 45). Patients with BMI less than 45 did not have a notable mortality benefit even 15 years after surgery.

Despite reservations regarding effects of bariatric surgery on mortality, it is clearly the most effective therapy for morbid obesity. It is, however, legitimate to ask whether bariatric surgery will have widespread impact on the prevalence of obesity given challenges of patient acceptance, postoperative management, cost, and provider reimbursement.

Pharmacotherapy

We do not yet have effective, safe pharmacotherapy for common human obesity. Drug therapy for obesity has been relatively ineffective or complicated by troublesome side effects. This has led to the suggestion that obesity is different from other chronic multifactorial diseases such as hypertension and hypercholesterolemia and will not lend itself to safe effective pharmacotherapy.³⁶ As a counterpoint, the history of antihypertensive and hypocholesterolemic therapy suggests that when we understand the biological mechanisms of a disease, effective treatment often follows. Once hypertension and hypercholesterolemia were recognized as risk factors, effective therapy emerged, but it took decades. Our understanding of the biology of obesity is very recent and still in a rapid growth phase. It should not prompt surprise or pessimism that safe effective pharmacotherapy has not yet emerged.

One question in treatment of obesity is potential effectiveness of monotherapy. Rosenbaum et al³⁶ argued that redundancy and interactions within the systems regulating appetite and metabolism make it unlikely that pharmacological manipulation of a single system will lead to long-term resolution of obesity. At first glance, this seems persuasive, but one

could have said the same thing about the treatment of hypertension 50 years ago. If ever there was a physiological variable regulated by redundant and interactive mechanisms, it is arterial pressure. Yet, we now have a number of effective monotherapies for hypertension. Beyond this, we have learned that multiple drugs are often needed for effective treatment of hypertension. There is no compelling reason why we should not be willing to consider combination drug therapy for obesity. There are promising recent developments in this regard.

Diet-induced obesity in rodents and common obesity in humans are accompanied by partial leptin resistance that limits therapeutic effectiveness of leptin. Amylin is a pancreatic hormone that is secreted with insulin.⁶¹ It inhibits appetite and promotes modest weight loss. It also increases leptin sensitivity. As a result, combination therapy with amylin and leptin acts synergistically to cause marked weight loss in diet-induced obese rats.⁶²

Despite the magnitude of the problem and bariatric surgery notwithstanding, we simply do not have a solution to the problem of obesity. We will make more progress by acknowledging this than we will by pretending that dietary and behavioral therapy is effective.

Sources of Funding

The author's research was previously supported by a Hypertension Genetics Specialized Center of Research (HL 550006) from the National Heart, Lung, and Blood Institute (NHLBI) and is currently supported by a Program Project Grant (HL 084207) from the NHLBI and by an endowment from the Roy J. and Lucille A. Carver Trust.

Disclosures

None.

References

1. Keith SW, Redden DT, Katzmarzyk PT, Boggiano MM, Hanlon EC, Benca RM, Ruden D, Pietrobelli A, Barger JL, Fontaine KR, Wang C, Aronne LJ, Wright SM, Baskin M, Dhurandhar NV, Lijoi MC, Grilo CM, DeLuca M, Westfall AO, Allison DB. Putative contributors to the secular increase in obesity: exploring the roads less traveled. *Int J Obesity*. 2006;30:1585–1594.
2. Zhang Y, Poenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. *Nature*. 1994;372:425–432.
3. Coleman DL. Effects of parabiosis of obese with diabetes and normal mice. *Diabetologia*. 1973;9:294–298.
4. Tartaglia LA, Dembski M, Weng X, Deng N, Culpepper J, Devos R, Richard GJ, Campfield LA, Clark FT, Deeds J, Muir C, Sanker S, Moriarty A, Moore KJ, Smutko JS, Mays GG, Wool EA, Monroe CA, Tepper RI. Identification and expression cloning of a leptin receptor, Ob-R. *Cell*. 1995;83:1263–1271.
5. Halaas JL, Gajiwala KS, Maffei M, Cohen SL, Chait BT, Rabinowitz D, Lallone RL, Burley SK, Friedman JM. Weight-reducing effects of the plasma protein encoded by the obese gene. *Science*. 1995;269:543–546.
6. Montague CT, Farooqi IS, Whitehead JP, Soos MA, Rau H, Wareham NJ, Sewter CP, Digby JE, Mohammed SN, Hurst JA, Cheetham CH, Earley AR, Barnett AH, Prins JB, O'Rahilly S. Congenital leptin deficiency is associated with severe early-onset obesity in humans. *Nature*. 1997;387:903–908.
7. Clement K, Vaisse C, Lahlou N, Cabrol S, Pelloux V, Cassuto D, Gourmelin M, Dina C, Chambaz J, Lacorte JM, Basdevant A, Bougneres P, Lebouc Y, Froguel P, Guy-Grand B. A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. *Nature*. 1998;392:398–401.
8. Farooqi IS, Wangenstein T, Collins S, Kimber W, Matarese G, Keogh JM, Lank E, Bottomley B, Lopez-Fernandez J, Ferraz-Amaro I, Dattani MT, Ercan O, Myhre AG, Retterstol L, Stanhope R, Edge JA, McKenzie S, Lessan N, Ghodsi M, De Rosa V, Perna F, Fontana S, Barroso I, Uddien DE, O'Rahilly S. Clinical and molecular genetic spectrum of congenital deficiency of the leptin receptor. *N Engl J Med*. 2007;356:237–247.

9. Farooqi IS, Jebb SA, Langmack G, Lawrence E, Cheetham CH, Prentice AM, Hughes IA, McCamish MA, O'Rahilly S. Effects of recombinant leptin therapy in a child with congenital leptin deficiency. *N Engl J Med.* 1999;341:879–884.
10. Yeo GSH, Farooqi IS, Aminian S, Halsall DJ, Stanhope RG, O'Rahilly S. A frameshift mutation in MC4R associated with dominantly inherited human obesity. *Nature Genetics.* 1998;20:111–112.
11. Farooqi IS, Keogh JM, Yeo GSH, Lank EJ, Cheetham T, O'Rahilly S. Clinical spectrum of obesity and mutations in the melanocortin 4 receptor gene. *N Engl J Med.* 2003;348:1085–1095.
12. O'Rahilly S, Farooqi IS. Genetics of obesity. *Phil Trans Royal Soc.* 2006;361:1095–1105.
13. Stunkard AJ, Sorenson TIA, Hanis C, Teasdale TW, Chakraborty R, Schull WJ, Schulsinger F. An adoption study of human obesity. *N Engl J Med.* 1986;314:193–198.
14. Borjeson M. The aetiology of obesity in children: A study of 101 twin pairs. *Acta Paediatrica Scand.* 1976;65:279–287.
15. Stunkard AJ, Foch TT, Hrubec Z. A twin study of human obesity. *JAMA.* 1986;256:51–54.
16. Stunkard AJ, Harris JR, Pedersen NL, McClearn GE. The body-mass index of twins who have been reared apart. *New Eng J Med.* 1990;322:1483–1487.
17. Allison DB, Kaprio J, Korkeala M, Koskenvuo M, Neale MC, Hayakawa K. The heritability of body mass index among an international sample of monozygotic twins reared apart. *Int J Obesity.* 1996;20:501–506.
18. Bouchard C, Tremblay A, Despres J-P, Nadeau A, Lupien PJ, Theriault G, Dussault J, Moorjani S, Pinault S, Fournier G. The response to long-term overfeeding in identical twins. *N Engl J Med.* 1990;322:1477–1482.
19. Levin BE, Triscari J, Sullivan AC. Relationship between sympathetic activity and diet-induced obesity in two strains of rats. *Am J Physiol.* 1983;245:R367–R371.
20. Levin BE, Dunn-Meynell AA. Defense of body weight against chronic caloric restriction in obesity-prone and -resistant rats. *Am J Physiol.* 2000;278:R231–R237.
21. Levin BE. The drive to regain is mainly in the brain. *Am J Physiol.* 2004;287:R1297–R1300.
22. Hill JO, Fried SK, DiGirolamo M. Effects of a high-fat diet on energy intake and expenditure in rats. *Life Sciences.* 1983;33:141–149.
23. Chang S, Graham B, Yakubu F, Lin D, Peters JC, Hill JO. Metabolic differences between obesity-prone and obesity-resistant rats. *Am J Physiol.* 1990;259:R1103–R1110.
24. MacLean PS. A peripheral perspective of weight regain. *Am J Physiol.* 2005;288:R1447–R1449.
25. MacLean PS, Higgins JA, Jackman MR, Johnson GC, Fleming-Elder BK, Wyatt HR, Melanson EL, Hill JO. Peripheral metabolic responses to prolonged weight reduction that promote rapid, efficient regain in obesity-prone rats. *Am J Physiol.* 2006;290:R1577–R1588.
26. Sturm R. Increases in clinically severe obesity in the United States, 1986–2000. *Arch Int Med.* 2003;163:2146–2148.
27. Friedman JM. A war on obesity, not the obese. *Science.* 2003;299:856–858.
28. Levine JA, Eberhardt NL, Jensen MD. Role of nonexercise activity thermogenesis in resistance to fat gain in humans. *Science.* 1999;283:212–214.
29. Bray GA, Champagne CM. Beyond energy balance: There is more to obesity than kilocalories. *J Am Dietetic Assoc.* 2005;105:S17–S23.
30. Levin BE. Metabolic imprinting: critical impact of the perinatal environment on the regulation of energy homeostasis. *Phil Trans Royal Soc.* 2006;361:1107–1121.
31. Barker DJ. The Wellcome Foundation Lecture, 1994. The fetal origins of adult disease. *Proc Biol Sci.* 1995;262:37–43.
32. Koza RA, Nikonova L, Hogan J, Rim J-S, Mendoza T, Faulk C, Skaf J, Kozak LP. Changes in gene expression foreshadow diet-induced obesity in genetically identical mice. *PLoS Genetics.* 2006;2:e81.
33. Dong C, Li W-D, Geller F, Lei L, Li D, Gorlova OY, Hebebrand J, Amos CI, Nicholls RD, Price RA. Possible genomic imprinting of three human obesity-related genetic loci. *Am J Hum Genet.* 2005;76:427–437.
34. Stunkard AJ. The management of obesity. *NY State J Med.* 1958;58:79–87.
35. Kramer FM, Jeffery RW, Forster JL, Snell MK. Long-term followup of behavioral treatment for obesity: Patterns of weight regain among men and women. *Int J Obesity.* 1989;13:123–126.
36. Rosenbaum MJ, Leibel RL, Hirsch J. Obesity. *N Engl J Med.* 1997;337:396–407.
37. Dansinger ML, Tatsioni A, Wong JB, Balk EM. Meta-analysis: The effect of dietary counseling for weight loss. *Ann Intern Med.* 2007;147:41–50.
38. Wilfley DE, Stein RI, Saelens BE, Mockus DS, Matt GE, Hayden-Wade HA, Welch RR, Schlechtman KB, Epstein LH. Efficacy of maintenance treatment approaches for childhood overweight: A randomized controlled trial. *JAMA.* 2007;298:1661–1673.
39. Rhodes ET, Ludwig DS. Childhood obesity as a chronic disease: Keeping the weight off. *JAMA.* 2007;298:1695–1696.
40. Tsai AG, Wadden TA. Systematic review: An evaluation of major commercial weight loss programs in the United States. *Ann Intern Med.* 2005;142:56–66.
41. Hill JO. Understanding and addressing the epidemic of obesity: An energy balance perspective. *Endocrine Reviews.* 2006;27:750–761.
42. Klem ML, Wing RR, McGuire MT, Seagle HM, Hill JO. A descriptive study of individuals successful at long-term maintenance of substantial weight loss. *Am J Clin Nutr.* 1997;66:230–246.
43. Tate DF, Jeffery RW, Sherwood NE, Wing RR. Long-term weight losses associated with prescription of higher physical activity goals. Are higher levels of physical activity protective against weight regain? *Am J Clin Nutr.* 2007;85:954–959.
44. Weinberg N, Mendelson M, Stunkard A. A failure to find distinctive personality features in a group of obese men. *Am J Psych.* 1961;117:1035–1037.
45. Friedman JF. Modern science versus the stigma of obesity. *Nature Medicine.* 2004;10:563–569.
46. Glucksman ML, Hirsch J. The response of obese patients to weight reduction: A clinical evaluation of behavior. *Psychosomatic Medicine.* 1968;30:1–11.
47. Hirsch J. Obesity: Matter over mind? *Cerebrum: The Dana Forum on Science.* 2003;5:7–18.
48. Leibel RL, Rosenbaum M, Hirsch J. Changes in energy expenditure resulting from altered body weight. *N Engl J Med.* 1995;332:621–628.
49. Dansinger ML, Gleason JA, Griffith JL, Selker HP, Schaefer EJ. Comparison of the Atkins, Ornish, Weight Watchers and Zone diets for weight loss and heart disease risk reduction: A randomized trial. *JAMA.* 2005;293:43–53.
50. Cummings DE, Weigle DS, Frayo RS, Breen PA, Ma MK, Dellinger EP, Purnell JO. Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. *N Engl J Med.* 2002;346:1623–1630.
51. Schwartz MW, Woods SC, Seeley RJ, Barsh GS, Baskin DG, Leibel RL. Is the energy homeostasis system inherently biased toward weight gain? *Diabetes.* 2003;52:232–238.
52. Berthoud H-R. Interactions between the “cognitive” and “metabolic” brain in the control of food intake. *Physiol Behav.* 2007;91:486–498.
53. Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrenbach K, Schoelles K. Bariatric surgery: A systematic review and meta-analysis. *JAMA.* 2004;292:1724–1737.
54. DeMaria EJ. Bariatric surgery for morbid obesity. *N Engl J Med.* 2007;356:2176–2183.
55. Sjostrom L, Lindroos A-K, Peltonen M, Torgerson J, Bouchard C, Carlsson B, Dahlgren S, Larsson B, Narbro K, Sjostrom CD, Sullivan M, Wedel H for the Swedish Obese Subjects Study Group. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *N Engl J Med.* 2004;351:2683–2693.
56. Dixon JB, O'Brien PE, Playfair J, Chapman L, Schachter LM, Skinner S, Proietto J, Bailey M, Anderson M. Adjustable gastric banding and conventional therapy for type 2 diabetes: A randomized controlled trial. *JAMA.* 2008;299:316–323.
57. Sjostrom L, Narbro K, Sjostrom CD, Karason K, Larsson B, Wedel H, Lystig T, Sullivan M, Bouchard C, Carlsson B, Bengtsson C, Dahlgren S, Gummesson A, Jacobson P, Karlsson J, Lindroos AK, Lonroth H, Naslund I, Olbers T, Stenlof K, Torgerson J, Agren G, Carlsson LM; Swedish Obese Subjects Study. Effects of bariatric surgery on mortality in Swedish Obese Subjects. *N Engl J Med.* 2007;357:741–752.
58. Adams TD, Gress RE, Smith SC, Halversen RC, Simper SC, Rosamond WD, LaMonte MJ, Stroup AM, Hunt SC. Long-term mortality after gastric bypass surgery. *N Engl J Med.* 2007;357:753–761.
59. Cummings DE, Flum DR. Gastrointestinal surgery as a treatment for diabetes. *JAMA.* 2008;299:341–343.
60. Sjostrom CD, Peltonen M, Wedel H, Sjostrom L. Differentiated long-term effects of intentional weight loss on diabetes and hypertension. *Hypertension.* 2000;36:20–25.
61. Roth JD, Coffey T, Jodka CM, Maier H, Athanacio JR, Mack CM, Weyer C, Parkes DG. Combination therapy with amylin and peptide YY [3-36] in obese rodents: Anorexigenic synergy and weight loss additivity. *Endocrinology.* 2007;148:6054–6061.
62. Roth JD, Roland B, Cole R, Coffey T, Cronister C, Weyer C, Baron A, Parkes D. Responsiveness to leptin restored by amylin in diet-induced obese (DIO) rats: Magnitude and mechanism of synergy. *Diabetes.* 2007;56:Suppl 1, A72.

Response to Dietary Therapy for Obesity: An Emperor With No Clothes

David W. Harsha, George A. Bray

Dr Allyn Mark's review of the literature involving the use of weight loss to improve blood pressure status uses as its linchpin the well established observation that maintenance of weight loss is difficult to achieve, especially through behavioral/lifestyle intervention approaches. We agree. Weight loss has been a particularly hard target for researchers, health professionals, and the public at large. This provides the impetus for other approaches including surgical and pharmacological procedures to address the issue.

Apparently there is no disagreement that weight loss does benefit one's blood pressure profile. The point of departure is one of degree of pessimism that behavioral and related interventions cannot succeed. We are more optimistic in this regard than Dr Mark.

As he has ably pointed out in his accompanying article, there are numerous biological, behavioral, and environmental paths to overweight. It is not surprising that the more or less "one size fits all" approaches that have been taken in past behavioral interventions have been less than impressive. Advances in tailoring the message and the behavioral intervention to individual characteristics are clearly needed but, we think, also clearly addressable. This is still a very immature field of research with much left to do.

Concomitantly, we are not averse to multi-therapeutic approaches. As with a number of behavioral conditions, combined medication and behavioral therapies may be the best approach, with surgery as the last resort in extreme cases.

In our view, the emperor's clothes are not so much the issue as the size of his tent.