Obesity: The Disease

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I. Introduction

Both increased body weight, as expressed in the body mass index [(body weight, kg)/(height, m)^2], and the waist circumference can be used to assess the risk of obesity, and both indices have been rising rapidly as the epidemic of obesity has increased over the past 20 years. Although obesity results from an imbalance between energy intake and expenditure, it is the connections between these two components of the first law of thermodynamics that can provide the clues about how we should understand, prevent, and treat this problem. An epidemiological model that describes the environmental factors that act on a susceptible host provides a useful framework for describing the current epidemic. The pathology of obesity can best be understood as an enlargement of fat cells and in some individuals an increased number of fat cells. These large fat cells release more fatty acids and a variety of cytokines that can provide a basis for understanding how obesity produces insulin resistance and changes in the inflammatory, thrombotic, and coagulation systems. Since no one wants to be obese, there is a large industry offering various forms of treatment. Though we can treat obesity with some success, we rarely cure it, and a plateau in body weight during treatment with subsequent relapse when treatment is terminated is the common experience. Surgical intervention with gastric bypass or gastric restriction is the most effective treatment but at an increased risk of mortality and with substantial morbidity. Only two pharmacological agents are currently approved for long-term use, and they produce only modest weight loss.

I start with the premise that all of us want to have a healthy weight and that no one wants to be obese. Interest in obesity has taken a sharp upturn in recent years, and the prevalence of this problem by any standards has increased rapidly. Obesity can be viewed as a chronic, stigmatized, neurochemical disease.[1] In this context, the goal is to return weight to a healthy level and to remove the stigma associated with the use of the word obesity. To consider it in the context of a neurochemical derangement has the advantage of focusing on the underlying mechanisms that produce the distortion in energy balance that produces the unhealthy state.[2]

II. Definition and Prevalence of Obesity

II.A. Body Mass Index. Throughout the past 50 years there has been a steady rightward, upward shift in the distribution curve for body weight. This trend can most effectively be traced using the body mass index (BMI), defined as the weight in kilograms divided by the height (in meters) squared (W/H^2), which provides a useful operating definition of overweight. A normal BMI is between 18.5 and 25 kg/m^2. A BMI between 25 and 29.9 kg/m^2 is operationally defined as overweight, and individuals with BMI > 30 kg/m^2 are obese, after taking into consideration muscle builders and other resistance-trained athletes. BMI also provides the risk measure for obesity.[3,4]

II.B. Central Adiposity. The waist circumference is a practical measure of central adiposity that is a surrogate for more precise measures of visceral fat such as a computed tomography (CT) or magnetic resonance imaging (MRI) scan of the abdomen at the L4-5 position. When BMI and waist circumference were used to predict the risk of hypertension, dyslipidemia, and the metabolic syndrome, the waist circumference was shown to be a better predictor than the BMI.[5,6]

II.C. Prevalence. From the BMI, it is clear that there is an epidemic of obesity that began in the 1980s and that continues unabated.[6] It affects children as well as adults. We are now seeing a rise in the prevalence of type 2 diabetes in adolescents that is directly related to obesity. Obesity has a higher prevalence in Latino and African-American populations.[7,8]

Recent data from the National Center for Disease Control show a continued increase in the prevalence of obesity. Both height and weight have increased in adults aged 20−74 between 1960 and 2002. Men increased in height from 68 in. (172.7 cm) to 69.5 in. (176.5 cm) and women from 63 to 64 in. (from 160 to 162.6 cm) during this period. For men weight rose from 166.3 to 191 lbs (from 75.4 to 86.8 kg) and for women from 140.2 to 164.3 lbs (from 63.7 to 74.6 kg), for an average increase of BMI from 25.2 to 28 kg/m^2 for men and from 24.8 to 28.2 kg/m^2 for women during this 42-year period. The increase in weight was greater in older men than in younger ones, but the reverse was true for women, with older women gaining less weight than younger ones. Similar effects are seen in children with the weight of 10-year-old boys rising from 74.2 lbs (33.7 kg) in 1963 to 85 lbs (38.6 kg) in 2002 and for 10-year-old girls rising from 77.4 lbs (35.2 kg) to 88 lbs (40 kg) in this same interval. These increases in weight were associated with increases in BMI for both boys and girls. For 7-year-old boys, BMI increased from 15.8 to 17.0 kg/m^2 between 1963 and 2002, and for 7-year-old girls it rose from 15.8 to 16.6 kg/m^2. For 16-year-old boys it rose from 21.3 to 24.1 kg/m^2 in this interval and for girls from 21.9 to 24.0 kg/m^2.[9]

II.D. Costs. Obesity is expensive, costing between 3% and 8% of health budgets.[10] Hospital costs and use of medication also increase with increasing BMI. In a large health maintenance organization, mean annual costs were 25% higher in participants with a BMI between 30 and 35 kg/m^2 and 44% higher in those with a BMI greater than 35 kg/m^2 than in individuals with a BMI between 20 and 25 kg/m^2.[11] Costs for lifetime treatment of hypertension, hypercholesterolemia, type 2 diabetes, heart disease, and stroke in men and women with a BMI of 37.5 kg/m^2 was $10 000 higher than for men and women with a BMI of 22.5 kg/m^2 according to data from the National Center for Health Statistics and the Framingham Heart Study.[12]

III. Etiology

III.A. Energy Imbalance. We become obese because over an extended period of time we ingest more carbon- and nitrogen-

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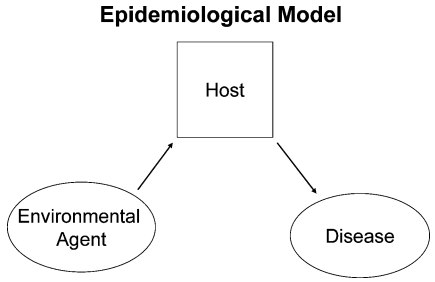

Figure 1. Epidemiological model of obesity. Environmental factors are shown interacting with the susceptible host to produce the disease called obesity.

containing compounds from food than we consume for energy. We and other animals thus obey the first law of thermodynamics, but this law fails to inform us on such important issues as how food intake is regulated, where fat is stored, and how genes control these processes.[13]

III.B. Epidemiological Model. An epidemiological model may be a better way than the energy balance model to conceptualize obesity as a disease.[1] In an epidemiological model, environmental agents act on a host to produce a disease (Figure 1). Disease is a function of the virulence of the agent and the susceptibility of the host. For obesity, the environmental agents include food, medications, toxins, physical inactivity, and viruses. In Western affluent societies, foods, particularly foods high in fat, are abundant, physical activity has gradually been reduced, and the "virulence" or "toxicity" of the environment has been heightened. For the genetically susceptible host, this excess of food energy, environmental toxins, and viruses, along with the reduced level of physical activity, may lead to an accumulation of fat in fat cells. Genetics loads the gun; the environment pulls the trigger.

III.C. Environmental Agents. III.C.1. Intrauterine Factors. Several intrauterine events influence postnatal weight and lifetime weight gain and fatness. These include maternal diabetes,[14] maternal smoking,[15] and intrauterine undernutrition,[16] all of which increase the individual's risk for increased body weight and diabetes later in life.

III.C.2. Neonatal Environment. Infants who are breast-fed for more than 3 months may have a reduced risk of future obesity.[17,18]

III.C.3. Adiposity Rebound. This is the age in childhood when BMI stops falling and begins to rise.[19] Early adiposity rebound predicts future obesity.[20]

III.C.4. Drug-Induced Weight Gain. In our current medicated society, it would not be surprising if drugs could account for weight gain. In most instances there are alternative strategies that can be used to treat a patient when their weight gain is closely associated with the initiation of a new medication for one of these conditions. Several receptors, especially the H_1, α_{1A}, and serotonins 2C and 6 (5-HT_{2C} and 5-HT_6) receptors, explain much of the weight gain associated with atypical antipsychotic drugs.[21]

III.C.5. Diet. Portion size,[22,23] fat intake,[24,25] and consumption of high fructose corn syrup (HFCS) in beverages[26] have all been implicated in the current epidemic.[27] Consumption of soft drinks predicted future weight gain in children and adults.[28−30]

III.C.6. Physical activity. Low levels of physical activity correlate with weight gain. In a 10-year study of individuals aged 20−74 in the National Health and Examination Survey (NHANES I) those with low levels of recreational activity gained more weight those those with higher levels.[31] Low levels of baseline energy expenditure predicted weight gain in the Pima Indians.[32] Exercise capacity and body composition predict mortality among men with diabetes.[33] Time spent watching television correlates with percent of overweight children.[34]

III.C.7. Smoking. Smokers have a lower body weight, and cessation of smoking is generally associated with weight gain.[35]

III.C.8. Viruses and Obesity. One laboratory has reported that obese humans have higher antibody levels to one strain of adenovirus (AM-36).[36]

III.D. Host Agents. III.D.1. Genetic Causes. The leptin gene, the melanocortin-4 receptor gene, the proopiomelanocortin (POMC) gene, and agouti gene have significant effects on body fat and fat stores. MC4-receptor defects may account for up to 6% of obesity in early onset, severely obese children.[37] Treatment of leptin-deficient children with leptin decreased body weight and hunger, indicating the importance of leptin for modulation of these processes in normal subjects. Heterozygotes for leptin deficiency have low but detectable serum leptin and have increased adiposity,[38] indicating that low levels of leptin are associated with increased hunger and gain in body fat. Leptin can also increase energy expenditure, and during reduced calorie intake, leptin attenuates the fall in thyroid hormones and the fall in 24-h energy expenditure.[39]

There are several rare clinical forms of obesity. The Prader−Willi syndrome is the most common. This disease is transmitted as a chromosome/gene abnormality on chromosome 15 and is characterized by a floppy baby that has difficulty feeding. These children are mentally slow, short in stature and obese.[40] The Bardet−Biedl syndrome is due, in at least one pedigree, to a defect in the chaperonin-like gene.[41]

The epidemic of obesity is occurring on a genetic background that does not change as fast as the epidemic has been exploding. It is nonetheless clear that genetic factors play an important role in the development of obesity, and over 90 genes have so far been implicated.[42]

III.D.2. Physiological Factors. This section will cover many of the most important physiological factors, but there are clearly others that we will not have space to discuss. The discovery of leptin in 1994 opened a new window on the control of food intake and body weight. The response of leptin-deficient children to leptin indicates the critical role that this peptide plays in the control of energy balance. Leptin enters the brain tissue, probably by transport across the blood−brain barrier. Once inside the brain, leptin acts on receptors in the arcuate nucleus to regulate in a conjugate fashion the production and release of at least four peptides. Leptin inhibits the production of neuropeptide Y (NPY) and agouti-related peptide (AGRP), both of which increase food intake while enhancing the production of pro-opiomelanocortin (POMC), the source of α-melanocyte stimulating hormone (α-MSH) which reduces food intake.[43]

Three other brain peptide systems have also been linked to the control of feeding. Melanin-concentrating hormone (MCH) is found in the lateral hypothalamus and decreases food intake when injected into the ventricular system of the brain.[44] Orexin (also called hypocretin) was identified in a search of G-protein-linked peptides that affect food intake. It also increases food intake and plays a role in sleep. Endocannabinoids (anandamide and arachidonyl 2-glycerol) also increase food intake by acting on CB-1 receptors. An antagonist to the CB-1 receptor has served as the basis for a new antiobesity drug.[45−48]

Gut peptides including cholecystokinin, pancreatic polypeptide, polypeptide YY, and enterostatin reduce food intake,[49] whereas ghrelin, a small peptide produced in the stomach, stimulates food intake.[43]

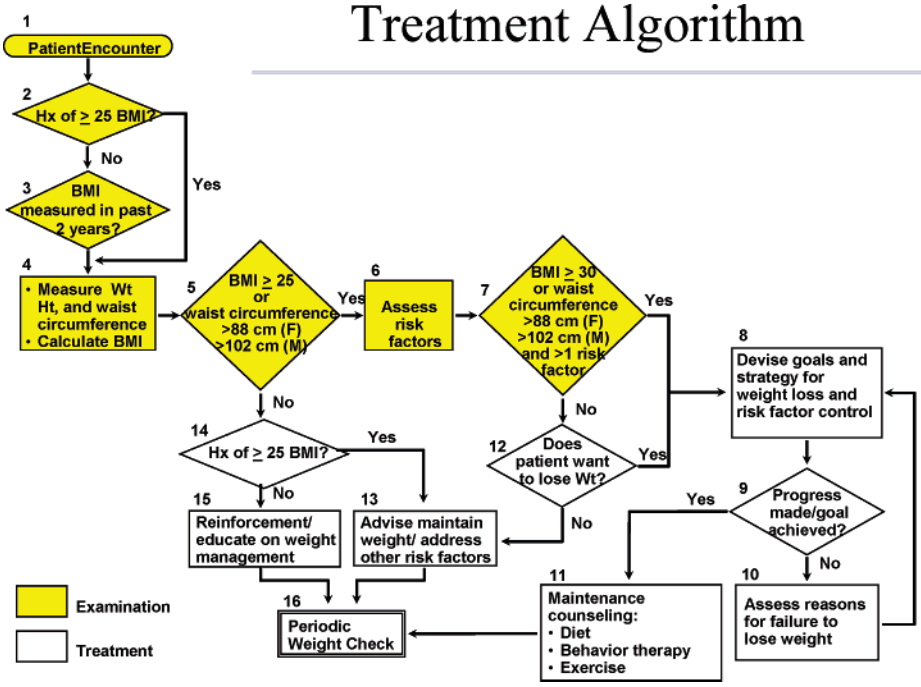

Figure 2. NHLBI algorithm for diagnosis and treatment of obesity, from National Heart, Lung, and Blood Institute/NIH.

Metabolism of fatty acids in the brain may be another important control point. A drug that blocks fatty acid synthase leads to significant weight loss. Malonyl CoA accumulates in this setting and has been suggested to be a molecule that modulates food intake.[50,51]

IV. Pathology of Obesity

Enlarged fat cells are the hallmark of obesity, and in some individuals there is also an increased number of fat cells.[52] It is the increased size of fat cells that is the characteristic pathology for obesity.

V. Pathophysiology

V.A. The Fat Cell as an Endocrine Cell. Two mechanisms can explain the pathophysiology of obesity. The first is increased fat mass, which can explain the stigmatization of physically obvious obesity and the accompanying osteoarthritis and sleep apnea. The second mechanism is the increased amount of peptides that is produced by the enlarged fat cells that act on distant organs. The discovery of leptin catapulted the fat cell into the arena of endocrine cells.[52] In addition to leptin, there are increased amounts of cytokines, angiotensinogen, adipsin (complement D), etc., and metabolites such as free fatty acids and lactate. In contrast to the other fat cell products, adiponectin release is decreased in obesity. The products of the fat cell in turn modify the metabolic processes in the host. For the susceptible host, these metabolic changes lead in turn to a variety of other processes, including hyperinsulinemia, atherosclerosis, hypertension, and physical stress on bones and joints.

V.B. Visceral fat. Considerable data suggest that visceral fat has a stronger relationship with the complications associated with obesity than total body fat.[53] Moreover, central adiposity is one of the key components of the metabolic syndrome whose other diagnostic criteria include the presence of low HDL-cholesterol, high triglycerides, high blood pressure, or elevated fasting glucose. These criteria are based on the recommendation of the National Cholesterol Education Program Adult Treatment Panel III.[54,55]

VI. Complications

VI.A. Death. The complications associated with obesity contribute to the 100 000 to 400 000 excess deaths per year.[56] Obesity is associated with a shortened life span. Using either the NCHS data or the Framingham data showed that a BMI of 30 or more reduces years of life by 3−5 compared to normal weight and that this effect has ethnic differences with black women showing fewer years of life lost for a given increase in BMI than black men, white men, and white women.[57,58]

VI.B. Diseases. The curvilinear "J"-shaped relationship of BMI to risk of complications, which has been known for 100 years, applies to Caucasian males more than Caucasian females and to a much lesser extent to African-American females.[59] Among Asians, the risk for diabetes at the same BMI is increased compared to Caucasians. The prevalence of diabetes mellitus is high in all ethnic groups, but the risk of cardiovascular events shows highly significant ethnic differences. Many kinds of cancers are related to obesity.[60] Recently, obesity has been added to the group of diseases where inflammatory markers are increased.[61,62]

VII. Prevention

A number of epidemiological studies have used the change in body weight as an end-point in the intervention. In contrast, a reduction in TV watching by children slows the gain in body mass index.[63] Among studies involving adults, there are unfortunately few successful programs. Another positive recent study showed that decreasing the consumption of "fizzy" beverages, primarily soft drinks, in children was associated with slower weight gain than in children who were not given this advice.[64]

VIII. Treatment

VIII.A. Realities of Treatment. The National Heart, Lung, and Blood Institute/NIH has provided an algorithm for evaluating the overweight patient. It is a useful framework on which to hang the information that is collected during the evaluation of individual patients (Figure 2).

Realism is one important aspect of treatment for obesity. For most treatments, including behavior therapy, diet, and exercise, the weight loss plateaus at less than 10% below the baseline weight. For many patients this is a frustrating experience, since their dream weight would require a loss of nearly 30% of their body weight. A weight loss of less than 17% would be a disappointment to women entering a weight loss program.[65] Yet, other than surgery, a weight loss of 10% is all we can do.[66] It is important for the patient and doctor to realize that an initial weight loss of 10% of body weight should be considered a success and that this amount of weight loss improves health risks.[67] Since obesity left to itself will contribute to a number of associated diseases, there are two therapeutic strategies. One could wait until associated diseases such as diabetes, hypertension, and dyslipidemia develop and treat them individually. Alternatively, and preferably, one would treat the obesity itself and in so doing reduce the risk of developing diabetes, hypertension, and other associated diseases.

VIII.B. Diet, Behavior Modification, and Exercise. Portion control is one dietary strategy with promising long-term results.[68] Other diets use low fat, low carbohydrate, or a balanced reduction of all macronutrients.[69] A meta-analysis of low fat versus conventional studies identified 5 studies lasting up to 18 months. In a comparison of the weight loss at 6, 12, and 18 months, there was no statistically significant differences from control, leading the authors to conclude that low-fat diets produce weight loss but not more so than other diets.[70] A recent study comparing a low-fat and low-carbohydrate diet where food was provided in excess showed that subjects eating the low-fat, high-fiber diet lost more weight than the control group.[71] Low-carbohydrate diets are the current rage. Several controlled trials of low-carbohydrate diets showed more weight loss with the low-carbohydrate than the control diet in the first 6 months[72−74] but no difference at 12 months.[72,75,76] In a head-to-head comparison of four popular diets, the average weight loss at 6 and 12 months was the same. The best predictor of weight loss for each of the diets was the degree of adherence to the diet.[77] Exercise has been an important component of weight loss programs, but when used alone, it has not been very successful.[78] The newest innovation in the use of lifestyle intervention is to implement it over the Internet. This has shown promising results.[79]

VIII.C. Medications. At present only two medications, sibutramine and orlistat, have been approved for long-term treatment of obesity, but several others are approved for short-term use. [80] Four others, diethylpropion, phentermine, phendimetrazine, and benzphetamine, are approved by the FDA for short-term use.

VIII.C.1. Noradrenergic Drugs. Phentermine, diethylpropion, phenmetrazine, and phendimetrazine are approved by the FDA for short-term use, usually considered to be up to 12 weeks. All of these drugs probably work by blocking the reuptake of norepinephrine into neurons. Phentermine is among the most widely prescribed appetite suppressants. Clinical trials with these drugs are usually short-term, which is why they are only approved for short-term use. Phentermine, a noradrenergic drug, has been used in combination with fenfluramine, a drug that blocks reuptake of serotonin and enhances its release. This combination proved to have serious side effects, producing left ventricular atrial regurgitation in up to 25% of the patients treated with this combination.

VIII.C.2. Sibutramine. Sibutramine significantly reduces the uptake of norepinephrine, serotonin, and dopamine by the preganglionic nerve endings and produces dose-dependent

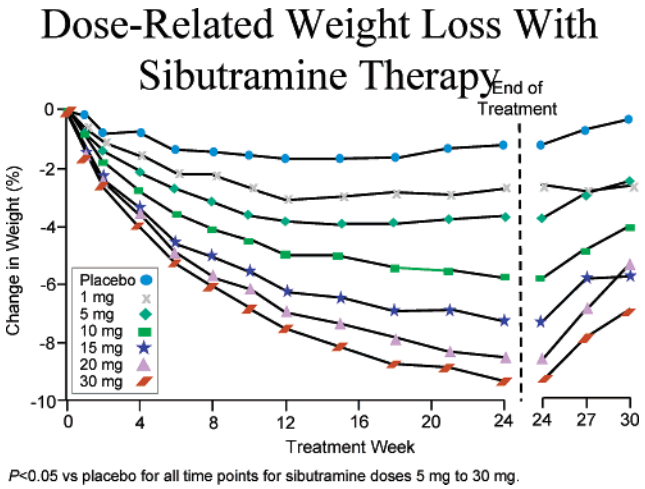

Figure 3. Effect of various doses of sibutramine on loss of body weight in a 6-month randomized placebo-controlled clinical trial. There is a clear dose response that has produced its maximal effect at all but the highest doses within the 6 months of this trial. When the trial was terminated, weight gains resulted as would be expected from an effective medication that was removed from use. Reprinted with permission from *Obesity Research* (1999, Vol. 7, No. 2, p 193). Copyright 1999 NAASO, The Obesity Society.

weight loss (Figure 3). The major drawback has been the small increase of blood pressure in some subjects. Two recent trials using sibutramine did not increase blood pressure in overweight hypertensive patients, who were treated for their hypertension with calcium channel blockers in one trial or β-blockers in the other.[81,82] In a 2-year trial, patients were randomized to sibutramine or placebo after a 6-month lead-in period of weight loss with sibutramine and diet. During the 18-month placebo-controlled period, the patients on sibutramine maintained essentially all of their weight loss. The placebo-treated group, on the other hand, regained nearly 80% of the weight they initially lost.[83]

VIII.C.3. Orlistat. Orlistat blocks intestinal lipase and thus enhances fecal loss of fat in the stools. There are now 4 trials with orlistat lasting 2 years each[84−87] and a recent trial lasting 4 years.[88] During the treatment period, patients on orlistat reached a maximum of 10% weight loss compared to about 5% with placebo. At the end of 4 years there was still a 2.5% difference in favor of orlistat. In the subgroup that had impaired glucose tolerance, conversion to diabetes was reduced by nearly 40%. Orlistat blocks triglyceride digestion and reduces the absorption of cholesterol from the intestine into the body accounting in part for the reduced plasma cholesterol found in patients treated with this drug.

One clinical trial added orlistat to patients who had been treated with sibutramine for 1 year, but there was no additional weight loss.[89]

VIII.C.4. Drugs Not Approved for Treating Obesity by the FDA. Clinical trials are available for several drugs that are not approved for treatment of obesity. Metformin produced a 1−3 kg weight loss over an average of 2.8 years in the randomized, double-blind, placebo-controlled Diabetes Prevention Program.[67] Although ephedrine combined with caffeine produced significantly more weight loss than either drug or placebo in a randomized, double-blind clinical trial conducted in Denmark, recent reports suggest that the herbal combination of ephedrine and caffeine may be hazardous,[90,91] and the Food and Drug Administration has removed these herbal combinations from the market place. Bupropion, which is marketed as an antidepressant and antismoking drug, produced significantly

more weight loss in a randomized 6-month clinical trial than placebo and maintained this weight loss for an additional 6 months.[92] Topiramate, a drug approved for treatment of epilepsy and migraine headaches, produced significant weight loss and significant side effects during clinical trials.[93] Zonisamide, another antiepileptic drug, also produced significant weight loss in a 4-month randomized clinical trial.[94] Ciliary neurotrophic factor (Axokine) produced weight loss of about 5 kg over 1 year in the 30% of patients who did not develop antibodies. Weight loss in those developing antibodies was not better than placebo.[95] Finally, rimonabant, an antagonist to the CB-1 receptor, administered to patients with dyslipidemia produced significant dose-related weight loss, decrease in triglycerides, increase in HDL-cholesterol, and reduction in blood pressure in a 1-year trial. It also showed promise as an antismoking drug.[96,97] For smokers, a combination of nicotine and caffeine might be useful.[98]

VIII.D. Surgery. Surgical intervention for obesity has become ever more popular.[99] The Swedish Obese Subjects Study has offered surgical intervention for obese Swedish patients aimed at reducing their obesity through a gastrointestinal operation. The control group includes obese Swedish patients who did not get surgical treatment but were treated with the best alternatives in the Swedish health care system. The effect of weight change on dyslipidemia, blood pressure, and insulin in the surgically treated group 2 and 10 years after operation was compared with the control group.[100] There was a graded effect of weight change on HDL-cholesterol, triglycerides, systolic and diastolic blood pressure, insulin, and glucose. By extrapolation from the degree of improvement in these comorbidities among the patients who lost weight, it cannot be long before this operated group will show a statistically significant improvement in longevity resulting from a treatment aimed specifically at reducing the mass of body fat. The challenge then will be to provide nonsurgical treatments that have dose-dependent effects on body fat stores, and thus the size of individual fat cells, as a treatment strategy aimed at reducing the complications of the disease of obesity.[100] A comparison of surgically treated and nonsurgically treated patients showed that weight loss improved long-term health outcomes but at a cost of significant short-term health problems.[101−103]

Biography

George A. Bray, M.D., graduated summa cum laude in chemistry from Brown University and magna cum laude in medicine from Harvard Medical School. Dr. Bray was executive director and professor at Pennington Biomedical Research Center from 1989 to 1999, where he continues his academic and research work as a professor of medicine. He has experience with surgical intervention for obesity when he was director of the Clinical Research Center at Harbor-UCLA Medical Center. He has experience with both inpatient and outpatient clinical research and has participated in several protocols evaluating the effectiveness of new pharmacological agents for treating obesity. Dr. Bray has received many honors and awards and is principal investigator on four NIH grants, including one MERIT Award. He has authored or coauthored more than 1500 publications.

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