Novel Approaches to the Reduction and Control of Body Fat Mass

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As the epidemic of obesity has grown over the past 20 years, the need to understand the elements of treatment has become more important. Along with this understanding will come novel ideas about techniques, strategies, molecules, and procedures that can be used to curtail the devastating effects of this epidemic. In this chapter, I will focus on five different approaches to treatment that encompass a classification for obesity based on a feedback model (1). These techniques include behavioral therapy, diet, exercise, medications, and surgery. Because there is only space for a brief discussion of each, the reader is referred to other sources for more detail (1–3).

Obesity is an imbalance between the energy that is ingested and the energy that is expended. This is simply another statement of the First Law of Thermodynamics. For any treatment to be effective, it must have an effect on one or both sides of this energy balance equation. The kinds of treatments discussed fall into two broad categories, depending on the degree of conscious effort needed to carry them out. Some are highly cognitive and require continuing the application of a set of activities. Others have a more physiologic, metabolic, or automatic component that will allow them to shift body weight and body fat stores unconsciously. One interpretation of the current epidemic of obesity is that it results from some "environmental" component that disconnects the regulatory feedback system by which intake and energy expenditure are regulated. We can overcome this by "conscious" or "cognitive" treatments, but ideally, we would like to identify the environmental factor(s) and by modifying them result in a more "automatic" adjustment in relation to food intake and energy expenditure that would regulate body fat stores at a normal level.

BEHAVIOR THERAPY

Over the past 30 years, there has been a steady improvement in behavioral techniques that were originally introduced only in 1967 by Stuart in a classic paper (4). The basic elements of any behavioral program focus on identifying the antecedents to eating, characterizing an individual's eating style and improving it, and providing rewards for changing behavior. With programs that last up to 24 weeks, the retention
is usually more than 75% and weight losses can be up to 10% of initial body weight (5). Retrospective analysis has shown that several strategies are particularly useful. These include self-monitoring of one’s eating habits, eating a lower-fat diet, being more physically active, and developing a support system to help reward successful behavior. Providing structured meal plans has proven an additional useful strategy (6). These can be either meal plans, menus, or portion-controlled foods. The use of the Internet has also proven to be a potentially valuable approach to delivering behavioral therapy (7). The major problem with behavioral strategies is that patients tend to regain weight after leaving the program. Recent focus has been on ways of continuing the program over longer periods.

Overweight adolescents are a good target for preventive strategies using behavior therapy, because good 10-year data show that intervention for this group can reduce the degree of overweight in adult life (8). Data on the efficacy of behavior programs carried out in controlled settings show that weight losses average nearly 10% in trials lasting more than 16 weeks (5,9). The problem with behavioral therapy is that regaining weight once the behavioral treatment ends is frequent. At least one long-term study showed that behavior therapy could provide long-term weight loss providing it was continued (10).

DIET

Calories

The essential element of any diet is that it reduces the total caloric intake. Many different diets have been recommended over the past 150 years since Mr. Banting published his famous pamphlet in 1863. One of the most popular themes has been the low carbohydrate diet (11). The fact that new diets continue to appear suggests that none of them has a magic formula because if one did, none of the others would have a successful market.

Fat

There are a number of elements of an effective diet that anyone can incorporate with potential benefit. The observation from behavioral therapy that a low-fat diet is what successful patients adopt suggests that this would be a useful strategy (12,13). Several reviews show that low-fat diets are associated with weight loss (14—16). The initial weight is one variable predicting the magnitude of the response (overweight people lose more than normal weight) and to the degree of fat reduction with another, with heavier people doing better. Palatability of the diet may be one factor. A recent study showed that replacing fat with olestra reduced body fat by nearly 20% over 9 months, whereas a reduced fat diet with the same available fat was relatively ineffective (17). However, a very low-fat diet can be difficult for many people to follow. For this reason, the best advice is to reduce saturated and trans-fatty acids, lower total fat to close to 25%, which is as palatable as possible for the individual.
Carbohydrate and Fiber

When the consumption of sugar and body weight are examined, there is usually an inverse relationship. However, there are recent data to suggest that the consumption of sugar-sweetened beverages in children may enhance the risk of more rapid weight gain. Both the baseline consumption and the change in consumption over 2 years were positively related to the increase in body mass index (BMI) over 2 years. That is, children who drank more sugar-sweetened beverages gained more weight and those who increased their beverage consumption had an even greater increase (18).

Both digestible and indigestible (fiber) can affect food intake (19,20). Although recent studies show that substituting starch for sugar does not produce greater weight loss (21), the type of digestibility of that carbohydrate may play a role. The glycemic load, that is the glycemic index times the carbohydrate load of a diet, may be important. In the Nurses Health Study, the glycemic load was related to the risk of developing heart disease (22) and diabetes (23). Diets with a low glycemic index, i.e., with lower increase in glucose, produce more satiety than diets with a high glycemic index.

Breast Feeding

Several recent studies suggest that the length of breast feeding affects childhood obesity. In a large German study of more than 11,000 children, von Kries et al. (24) showed that the duration of breast feeding as the sole source of nutrition was inversely related to the incidence of obesity, defined as a weight above the 95th percentile, when children entered the first grade. In this study, the incidence was 4.8% in children with no breast feeding, falling in a graded fashion to 0.8% in children who were solely fed from the breast for 12 months or more. A second large report (25) also showed that breast feeding reduced the incidence of overweight, but not obese adolescents. The third report with fewer subjects and more ethnic heterogeneity failed to show this effect (26). However, the potential that breast feeding can reduce the future risk of obesity is another reason to recommend breast feeding for at least 6 to 12 months.

Dietary Calcium

Nearly 20 years ago, McCarron et al. (27) reported that there was a negative relationship between BMI and dietary calcium intake in the data collected by the National Center for Health Statistics. More recently, Zemel et al. (28) found that there was a strong inverse relationship between calcium intake and the risk of being in the highest quartile of BMI. These studies have prompted a re-evaluation of studies measuring calcium intake or giving calcium orally. In the prospective trials, subjects receiving calcium had a greater weight loss than those receiving placebos. Increasing calcium from 0 to nearly 2000 g/d was associated with a reduction in
BMI of approximately 5 BMI units (29). These data might suggest that low calcium intake was playing a role in the current epidemic of obesity.

EXERCISE

Exercise is an obvious way to increase energy expenditure. This is desirable for all Americans and would be beneficial for reducing cardiovascular risks (30). However, for many people who are overweight, exercise can be a challenge, because they are already expending more energy doing everyday activities. Thus, for many such patients, a simple walking program can be the best approach. That this is valuable is shown by the Finnish Diabetes Study (31) and the Diabetes Prevention Program (32), where a lifestyle program of diet and exercise produced a 58% reduction in the conversion of patients with impaired glucose tolerance to diabetes mellitus.

If exercise is substantial and supervised, increases in weight loss can be demonstrated. However, for many people, exercise adds little extra weight loss to that produced by a diet program. Some reports suggest that exercise may conserve body protein during dieting, but others do not.

The most beneficial part of an exercise program comes when trying to maintain a lower body weight. In a survey of people who were successful in maintaining weight, exercise was maintained at a level significantly above people without a weight problem (12).

MEDICATIONS

Medication should be seriously considered for clinically overweight individuals in this group. Two strategies can be used. The first is to use drugs to treat each comorbidity, i.e., individually treating diabetes, hypertension, dyslipidemia, and sleep apnea. Alternatively, or in addition, patients with a BMI greater than 30 kg/m² could be treated with antiobesity drugs. Current drugs include appetite suppressants that act on the central nervous system, and orlistat, which blocks pancreatic lipase. The availability of these agents differs from country to country, and any physician planning to use them should be familiar with the local regulations. Most of the drugs on the market were reviewed and approved more than 20 years ago, and are approved for short-term use only (1). The basis for the short-term use is twofold. First, almost all the studies of these agents are short term. Second, the regulatory agencies are concerned about the potential for abuse, and thus have restricted most of them to prescription use with limitations. The withdrawal of fenfluramine and dexfenfluramine from the market in 1997 following in the development of valvular heart disease further compounds the concern of health authorities about the safety of these drugs (33). Because of the regulatory limitations and the lack of long-term data on safety and efficacy, the use of the drugs approved for short-term treatment must be carefully justified. They may be useful in initiating treatment and in helping a patient who is relapsing.
Sibutramine (Meridia®; Reductil) is approved in most countries for long-term use. The evidence shows a dose-related weight loss that can reach 10% or more (34,35). The side effect profile includes dry mouth, asthenia, insomnia, and constipation. It also produces a small increase in heart rate of between 2 and 5 beats a minute, and a small increase in blood pressure of between 2 and 4 mm Hg. Clinical data show no evidence of valvulopathy. Blood pressure should be followed carefully, and the drug may be inappropriate in patients with stroke, congestive heart failure, or recent myocardial infarction. It should not be used with other serotonergic drugs or drugs that inhibit monoamine oxidase.

Orlistat (Xenical®), a drug that blocks intestinal lipase, has been approved for long-term use in most countries. In clinical trials lasting up to 2 years, orlistat was associated with a mean weight loss of up to 10% at the end of 1 year in patients who were prescribed a 30% fat diet (36,37). As might be expected, because the drug blocks pancreatic lipase in the intestine, fecal fat loss is increased. Major side effects reported early were markedly reduced over time, implying that patients learned to use the drug effectively in relation to dietary intake of fat. The effective use of this medication requires that physicians and their staffs provide good dietary control counseling to patients.

The combination of ephedrine and caffeine is a third compound for which a randomized clinical trial has been published (38). Over 6 months, the patients treated with ephedrine and caffeine lost more weight than the placebo-treated group, or the two groups treated individually with ephedrine or caffeine. This research has been used for marketing of herbal preparations that contain ephedra alkaloids with or without caffeine. One published clinical trial has shown significantly greater weight loss with an herbal ephedra/caffeine preparation than with placebo (39). Several companies have programs to develop chemicals that mimic the effect of these \( \beta_3 \) adrenergic receptors (40).

The epidemic of obesity, the discovery of genes that produce obesity (3), and a slim armamentarium for treatment of obesity have spurred many pharmaceutical companies to search for new agents (1). These can be divided into two categories: compounds that are in clinical trials with suggestive data and new molecules just entering the clinical arena. In the former category are bupropion, leptin, topiramate and androgens. Bupropion is a US Food and Drug Administration (FDA)—approved anti-depressant that produces weight loss according to a recently published paper (41). Leptin is the peptide that when deficient, produces massive obesity in mice and in a few human families. These patients respond to leptin with weight loss suggesting that leptin might be clinically useful if the proper way of delivering it can be found (42). The third molecule, topiramate, is an anti-convulsant approved by the FDA for this purpose. Several studies now suggest that topiramate produces weight loss in patients receiving it for their epilepsy. Clinical trials with this compound are currently under way (43). Finally, androgens have been shown to reduce visceral fat when applied to the skin of mildly hypogonadal men (44) and new agents modulating the 11-\( \beta \)-hydroxysteroid dehydrogenase may provide a newer strategy to reduce visceral fat (45).
A number of other molecular targets could serve as the basis for clinically useful drugs (46). These molecules can be divided into those that have a peripheral mechanism of action and those that act on the brain. Thermogenic β-adrenergic agonists are one target that have been investigated for more than 15 years, but as yet no clinically useful molecule has been identified (40). Cholecystokinin reduces food intake in animals and man. To date no useful molecules have been identified that work through this receptor. Glucagon-like peptide-1 (GLP-1) is processed from the enteroglucagon molecule by gastrointestinal cells. Infusion of GLP-1 into lean and obese human beings reduces food intake and molecules to this receptor system are under development (47). Ghrelin, produced primarily in the stomach, has been recently identified and shown to increase food intake when given peripherally or centrally (48). Antagonists to this receptor system offer potential for future molecules to treat obesity. Finally, the pentapeptide enterostatin, cleaved from procolipase in the intestinal lumen, reduces food intake and primarily fat intake (49). This or similar molecules might have interesting potential for modulation of clinical fat intake.

Neuropeptide Y is one of the most potent stimulators of food intake known (46). Several abstracts suggest that this may be a useful target, with molecules aimed at either the Y-1 or Y-2 receptor. Loss of the melanocortin-4 receptor produces massive obesity in mice, suggesting that molecules aimed at this receptor could be useful. One of these molecules α-melanocyte stimulating hormone (α-MSH), is the agonist produced from pro-opiomelanocortin (POMC). An endogenous molecule, agouti-related peptide (AGRP) inhibits the effect of α-MSH. Modulation of agrp or α-MSH would be two potential targets. The peptides mentioned previously are under control by circulating leptin acting on receptors in the arcuate nucleus of the hypothalamus. The fourth peptide found in this system (NPY, AGRP, α-MSH) is a cocaine-amphetamine regulated transcript (CART). As an inhibitor of food intake, it would need a receptor agonist to be effective. At least two other hypothalamic peptides need to be considered in this discussion. The first is melanin-concentrating hormone (MCH). Animals overexpressing this peptide are heavier than controls and disabling the production of this peptide produces leanness. Another hypothalamic peptide is corticotrophin-releasing hormone (CRH) and urocortin, two variants that differentially bind to CRH-R1 and CRH-R2. CRH reduces food intake and modulating its activity would be another potential mechanism.

SURGERY

Surgical intervention was initiated more than 40 years ago with operations that shortened the absorptive surface available to gastrointestinal contents by various bypass operations. At present, the principal operations are the gastric bypass; the vertical banded gastroplasty; and the gastric band, which allows a constrictive band around the stomach to be expanded by injecting saline into a subcutaneous reservoir. With the introduction and advancement in the skill of surgeons using laparoscopic surgery during the 1990s, the safety of these procedures improved. Although originally recommended for people with a body mass index above 40 kg/m², the studies
showed marked benefits to patients having this surgery and suggest that the BMI should be reduced to 35 kg/m² or even lower if there are significant risks associated with the obesity (50,51).

SUMMARY PERSPECTIVE

In this discussion, I have examined a number of strategies of correcting the imbalance between energy intake and energy expenditure. These strategies are grouped into those that require predominantly cognitive or conscious activity and those that are more automatic. Behavioral therapy is a prime example of a cognitive strategy because implementation of these techniques requires instruction. Whether they involve direct interaction with an instructor, the Internet, or a manual, they involve conscious choices to modify behavior. Changing levels of physical activity are also cognitive, because it is the conscious act of the individual who chooses to walk up stairs rather than take the elevator or escalator. Diets, on the other hand, can be cognitive or physiologic, metabolic or automatic. Portion control would be a good example of a "conscious" or cognitive strategy. Breast feeding is cognitive for the mother, but not for the infant where the longer the breast feeding the lower the body weight for height at entry to school. Similarly a high calcium intake, choosing foods with a low glycemic index, and eating low-fat diets would each have a cognitive and an automatic component. When olestra is added to the diet, this effect would be more automatic or physiologic rather than cognitive. Medications require the conscious effort to take them, but when effective they show a dose-related decrease in body fat, meaning that they have an underlying physiologic or pharmacologic effect that is "automatic" rather than cognitive. Surgery requires the decision to undergo an operation, but the long-term weight loss afterward can be viewed as the physiologic response to the changes in gastrointestinal function that are generated by the surgery. What is needed is a clear understanding of how automatic strategies can be identified and implemented on a wide basis to prevent the epidemic of obesity, and to treat those individuals whose obesity we cannot prevent.

REFERENCES


DISCUSSION

Dr. B. S. Ramakrishna: You referred to an inverse association between calcium intake and body weight. And from the previous talk by Professor Langhans, we understood that calcium blocking could inhibit anorexia. Do we know the mechanisms for this and can calcium be used in practice to reduce body weight?

Dr. George A. Bray: For the data on calcium, I'll refer you to the best set of studies that I know. This is a paper by Davies in The Journal of Clinical Endocrinology and Metabolism, December 2000. They looked at their set of patients who have been treated mainly for osteoporosis with graded levels of calcium, and it's clear from their data that either adding calcium, or your base line calcium intake, were related to your BMI. Now these weren't obese people. There is as yet no data on obesity anywhere. There are trials underway, because calcium intake in the United States is not as high as it might be for many reasons, particularly osteoporosis in women, but there are as yet no data from obese individuals, only the epidemiologic population-based or osteoporosis-based sets that I've shown you, but because it's a non-toxic agent, because it's beneficial for other potential effects unless you're a renal stone former, it has a great potential for being one of those automatic modulators of this coupling between intake and expenditure, which we badly need, if we're going to heal this world-wide epidemic. I would take a look at that paper by Davies. It's clear. It's in my paper.

Dr. Marcello Giovannini: In your talk, I would like your opinion about the role of functional
lipids like medium-chain triglyceride in conjugated linoleic acid and omega 3 long-chain polysaccharide fatty acids. And I have a problem. You spoke about the Von Kries’ paper (1), and I completely agree about the regulation for the human milk, but in human milk you have low protein, and with the formula fed to all the children the protein intake was very high. For these reasons, even if more studies are needed, we agree completely that the intake of protein in the first year of life may develop obesity. Finally, what kind of product is olestra, because it is a substitute for lipids, is it a protein or if not, what is it?

Dr. George A. Bray: I’m not sure I got your very first one. Were you talking about conjugated linoleic acid? Actually, I left out my slide on conjugated linoleic acid. I think it’s a very interesting conjugation. Conjugated linoleic acid means just moving the double bonds by one carbon in the chain of 18 carbons and, therefore, with these isomers, one of them is the important one, the other three are not very important. There are actually some data to suggest that body weight and body composition may be altered. There are also some concerns about some toxic issues with it, and I didn’t include it, but it is another interesting manipulation of fatty acids, and I think there are a lot of interesting things about fatty acids that I could spend a good deal of time on. I think they are important, especially specific ones, and that’s a good example. Your question about human milk intake. I used it as a jumping-off point for the calcium story. What it is about the human milk intake over prolonged periods that led to a much smaller percentage of children being overweight in Germany at school entry and actually beyond that, some of these studies go on into early adolescence now, isn’t clear. It could be protein. It could be the anions that are present I don’t know what it is, but it’s an automatic response. It’s something that leads to a long-term change in the coupling between intake and expenditure and is the kind of thing we need as a preventive strategy, if we’re going to change the obesity epidemic that we have. On your question of olestra, olestra is sucrose polyester. It’s taking sucrose and then coupling either seven or eight hydroxyl groups with fatty acids and the characteristic of the lipid depends upon the kind of fatty acids that are used. It can be liquid or it can be solid at room temperature, depending on the kind of fatty acids that are on this sucrose backbone. It is indigestible by intestinal lipases, so when you eat olestra, you’re basically putting in an indigestible lipid that is not absorbed or digested and passes out in the stools. If you use too much of it, you could get a fecal fat loss. But with the doses we were working with, that isn’t a problem, and that’s in part why we selected the doses and concentrations that we use. Does that help you with it?

Dr. Gareth Williams: Just a comment about the breast feeding and then a question. The kind of mother that takes the baby off the breast and parks it with a bottle of milk is probably the same kind of mother that’s happy to park the child in front of the television in years to come, so my guess is it’s a behavioral thing to do with the mother in the family environment, rather than any beneficial quantities of x, y, and z in breast milk. My question relates to the diabetes prevention program. What do you think is going to happen to the people, now that they’ve come off the end of the terminated 4-year study? Do you think you’ve actually reduced the risk in the long-term in the Metformin group by a third, then in the lifestyle group by 80% or 60% or whatever, or do you think you’ve simply delayed it by a year or two and will the diabetes catch up with them in the end?

Dr. George A. Bray: Your question is a good one. We’ve just been funded for the first 5-year follow-up and we plan actually 10 years of follow-up for this work, because it’s an intensively studied group of nearly 3000 people. As you probably know, although most of you don’t, there was a Troglitazone arm in that trial initially, which I didn’t include. And that group was taken off Troglitazone, when it was removed from the market. Their conversion rate of Troglitazone was almost the same as the Metformin one. So for a period of time and
the average is about a year and a half off. They had the same low rate as the Metformin group, although their weights had begun to come up. We are not discontinuing Metformin, so we will not know whether we would have prevented it for a long time or not, because we're continuing that therapy, because it seemed ethically appropriate to do so. We did discontinue the Metformin for a short period as a washout, to see whether we were simply masking diabetes or not. We are not. That now seems clear, but we will not know if we had stopped it, we would have a low rate, which we do know for Troglitazone. We have a lifestyle group again, because our advisory board said you must offer lifestyle to everybody. It is unethical having found an effective therapy not to do that, so for the current 6 months to July 2002, all of our participants are receiving, if they wish, an intensive lifestyle program. Then in July, we will have to reduce that, because we don't have enough money to continue it. But we will be continuing to follow them with a lower level of lifestyle, so ask me in 5 years and I'll tell you what we've learned, but that's where we are and that's where the trial's going.

Dr. Peter Nieman: Is it important or how important is it to differentiate between glycemic load and glycemic index? Is that an important distinction, yes or no?

Dr. George A. Bray: The glycemic index is this rise in glucose, the glycemic load is the glycemic index times the quantities you eat. They both seem to work in clinical trials. The epidemiological ones, at least the Boston group, have tended to use the glycemic load as their preferred one. I can't see a difference in the longer-term trials using one or the other. And they suggest that there are benefits for diabetes and other conditions, the data for which I didn't show you. I can't see a difference in which one you choose. Do you have a preference?

Dr. Rinaldo Zanini: You've shown many interesting data about weight loss. Do you have any concerning the years of life gained using programs for losing weight?

Dr. George A. Bray: The quality years of life increased? The problem is we don't have long-term data. You can extrapolate from the short-term weight losses as though someone maintained that for a long period of time, but the probability is, if you look at the weight regain, that people don't maintain long-term weight loss when they're taken off treatment, so there really isn't any data available to answer your question from a treatment perspective. Now there are some interesting data again from these epidemiologic studies, showing that people whose weight goes up have a deterioration in the quality of life, while people whose weight has come down have an improvement in the quality of life in a variety of different indices, so my expectations would be that if we could develop effective long-term strategies, there would be improvements in the quality of life, but the data using treatment strategies as opposed to epidemiologic follow-up strategies aren't available to my knowledge.

Dr. Marcello Giovannini: Somebody spoke before about glycemic index. And I appreciate your data about breakfast. Do you know what to you use or to recommend for use at breakfast, is it corn flakes? Because the data of Jenkins show that corn flakes have the highest glycemic index among many other products and there is also the question of the quality of the carbohydrate. When you spoke about complex carbohydrates, I come from a country, where we use complex light carbohydrates like pasta, but the quality of the glycemic index depends how the pasta is cooked, because if you eat pasta in some other places outside Italy, you have a lot higher glycemic index. Also in our country, in the north it is higher and in the south it is lower. This depends on the recommendation on how to cook the food, but please answer about the breakfast especially and the glycemic index of some cereals.

Dr. George A. Bray: The glycemic index issue generates a lot of discussion of which your points, Sir, are quite good ones. There is at the moment discussion in the dietary allowance committees in the United States about whether to advise people on glycemic index foods and
their intake. Your point about the glycemic index changing as a function of cooking and how you prepare foods is a very good one and is part of the reason that a number of people have spoken against trying to make advice to the public about glycemic index foods, because they are so dependent upon a lot of preparation issues and the kinds of things that are in them. My point about them was that if you make comparisons where the data are clear, you do see some indications that the low glycemic foods have a different impact on intake than the higher glycemic ones, but in day-to-day status, it’s difficult to implement, and I recognize that problem.

Dr. Margriet S. Westerterp-Plantenga: I wondered from those long-term studies that you showed, it seemed that the weight regain was inversely correlated with weight loss. Are you aware of any analysis of that? And also, could you comment on comorbidities during weight regain?

Dr. George A. Bray: I don’t know of any analysis on the weight regain versus loss issue. The only studies that come to mind are ones where Tom Wadden compared very low-calorie diets and then followed those versus a standard diet reduction. And you get more weight loss in one, but if you follow them out for a year, they’re at exactly the same point. The challenge in most of the follow-up studies is to get people to come back, and it’s a challenge in all of our weight loss studies, because you presume that, when people stop coming back, they’re on an upward trend, so our regulatory bodies require us to do what’s called last-observation-carried-forward, as though the last time you saw them was where they would have been 2 years later. That’s almost certainly not the case, and I don’t find it a very informative analysis. I suspect people who disappear from trials regain weight. The informative information, about what happens to people who complete at the other end, concerns people who actually got there, and your last-observation-carried-forward analysis is dependent upon when people drop out of a study. If you have a lot of drop-outs at the beginning, that biases it badly against you for weight loss, but if they all drop out in the last month, it has no impact at all. So I think this issue of long-term follow up and what happens to people is difficult. Population wise, of course we’re all going this way, so I suspect that this is the general upward trend. Regarding comorbidities on weight gain, there was considerable interest in the phenomenon of weight cycling, going up and down and weight regain causing more problems, making it is more difficult to lose weight. The National Institute of Health appointed a task force, which still operates and one of the things that they did was to look at all of the data around this issue of weight loss, weight regain and cycling and whether it was detrimental or not detrimental, and they concluded that the impact on comorbidities with weight regain, or the alleged impact, was not demonstrated. They really felt that the American press had made a big story out of the weight cycling phenomenon and to a far greater extent than the data warranted. So that wasn’t part of that analysis, but I think I subscribe to it.

Dr. Roger J. Glass: You gave such a wonderful, clear, and optimistic view of interventions of drugs, of diet, of exercise or cognitive functions to reduce body mass, and at the end you concluded with this terribly pessimistic thing that only surgery would work. So my question is: are there other comorbidities besides diabetes, like improvements in lipid profile or cardiovascular outcome, that come with some of these diets. Has that been studied and would that be another way to improve or introduce these?

Dr. George A. Bray: The comorbidities improve with weight loss almost in a weight dependant fashion, and what the diabetes prevention program showed was that weight reduction of 3%, for example, for the Metformin or 7% for the lifestyle group, produced quite dramatic reductions in conversion rates to diabetes. There are a number of non-pharmacological lifestyle intervention programs for hypertension, which show that you will reduce the
amount of medication, you will reduce the blood pressure, and that as long as your weight stays down, your blood pressure dramatically improves. So weight loss of modest degrees, here 3% to 7%, can have significant effects on comorbidities. The impact on cholesterol, however, is not very great with weight loss. To get a reduction in cholesterol, you need to have a major weight loss, and this is the reason I didn’t deal with surgery. However, in the surgical studies that are going on in Sweden, where there are a thousand operated and a thousand matched controls who were treated in the standard Swedish health care system, where these subjects are matched on 28 variables, they are quite closely matched groups. The improvement in hypertension triglycerides risk for diabetes or conversion to diabetes in the surgical group is dramatic, particularly diabetes. Interestingly, blood pressure comes down and then goes back to normal after 6 years, even though weight remains low. To get a reduction in cholesterol, it takes a weight loss of 30 kg at a stable level to be achievable. But for HDL cholesterol, every small reduction increases it. For triglycerides, every small weight reduction decreases them, so there are clear reductions in most comorbidities with even modest weight losses. The challenge, I think, is to implement and maintain these. The lifestyle program DPP is very expensive. We’ll surely never translate that, at least not in that form.

REFERENCE