

Clinical Lipidology Roundtable Discussion

JCL Roundtable: Clinical management of individuals with obesity

W. Virgil Brown, MD*, Harold Bays, MD, George A. Bray, MD, MACP

Emory University School of Medicine, 3208 Habersham Rd, NW, Atlanta, GA 30305, USA (Dr. Virgil Brown); Louisville Metabolic and Atherosclerosis Research Center, 3288 Illinois Avenue, Louisville, KY 40213, USA (Dr. Harold Bays); and Pennington Biomedical Research Center/LSU, 6400 Perkins Road, Baton Rouge, LA 70808, USA (Dr. George A. Bray)

KEYWORDS:

Obesity;
Diabetic;
Adiposopathy;
Intervention;
Weight

Abstract: Our topic is the evaluation and treatment of obesity in the practice of medicine. I am joined by Dr. Harold Bays who has carried out many studies of dietary and medical interventions in patients with obesity. I am also honored to have Dr. George Bray who is known for his many years of research into causes of obesity and its therapy. Our goal is bring this clinical and research experience to bear on the office practice of medicine.

© 2014 National Lipid Association. All rights reserved.

Financial disclosures

Dr. Bays has received research grants from Alere, Amarin Corp., Amgen Inc., Ardea Inc., Boehringer Ingelheim, California Raisin Board, Catabasis Pharmaceuticals, Inc., Eisai Co., Ltd., Elcelyx Therapeutics, Inc., Eli Lilly and Company, Esperion Therapeutics, Inc., Forest, Gilead, Given, GlaxoSmithKline, High Point Pharmaceuticals, LLC, Hoffman-La Roche, Home Access, Isis Pharmaceuticals, Inc., Janssen Pharmaceutical Companies, Merck & Co., Inc., Micropharma Limited, Nektar, Novartis Corporation, Omthera Pharmaceuticals, Orexigen Therapeutics, Inc., Pfizer, Inc., Pronovo, Regeneron Pharmaceuticals, Inc., Takeda Pharmaceutical Company, TIMI, TransTech Pharma, Inc., Trygg Pharma, VIVUS Inc., WPU, and XOMA Ltd. Dr. Bays has received honorarium from Amarin Corp., Amgen Inc., AstraZeneca, Bristol-Myers Squibb Company, Catabasis Pharmaceuticals, Inc., Daiichi Sankyo, Inc., Eisai Co., Ltd., Isis Pharmaceuticals, Inc., Pronovo, VIVUS Inc., and WPU.

Dr. Bray has received honorarium from Herbalife Nutrition Council and Medifast Advisory Board.

Dr. Brown: Our topic is the evaluation and treatment of obesity in the practice of medicine. I am joined by Dr. Harold Bays who has carried out many studies of dietary and medical interventions in patients with obesity. I am also honored to have Dr. George Bray who is known for his many years of research into causes of obesity and its therapy. Our goal is bring this clinical and research experience to bear on the office practice of medicine. All physicians know that this is an important area of concern but often find that the application of therapy is not successful.



Dr. Brown

I would like to start our discussion with the description of a patient representing a very common presentation. This is a 55-year-old postmenopausal woman, 5 feet 8 inches (1.73 m) tall with a waist size of 43 inches (99 cm) and body weight of 264 pounds (120 kg). Blood pressure is 140/90 mm Hg. Her body mass index (BMI) is 40. Her fasting plasma glucose is 105 mg/dL. Total cholesterol 225, high-density lipoprotein cholesterol 35, and low-density lipoprotein cholesterol 140 mg/dL. The plasma triglycerides are 250 mg/dL. And my first question is, what further

* Corresponding author.

E-mail address: wbrown925@bellsouth.net

Submitted February 7, 2014. Accepted for publication February 10, 2014.

information do you need about this woman to provide a plan to deal with her obesity? Dr. Bays, do you want to start?



Dr. Bays

supported by findings consistent with adverse metabolic consequences (eg, elevated glucose levels [possible prediabetes mellitus], high blood pressure, and the typical adipopathic dyslipidemia [sometimes called “atherogenic dyslipidemia,” although admittedly, elevated cholesterol alone can also be “atherogenic”]). Given this presentation, the focus should not only be on the weight of the patient, but also on the health of the patient.¹

Dr. Brown: I assume this would focus on cardiovascular risk?



Dr. Bray

Dr. Bray: You’d get an electrocardiogram. Because this woman is significantly overweight, you’ll need to know how well she performs. If you’re going to have her exercise, at her age, which is 55, you might want to evaluate her cardiovascular competence with an exercise tolerance test because she’s is substantially over-

weight and she might well have some limitation that you’d want to consider. People at this age and of this gender have a substantially increased risk of gallstones, and I think that would be worth evaluating because 1 of the issues that can occur during weight loss particularly relatively rapid weight loss, is cholecystitis, which is usually caused by cholesterol gallstones.

Dr. Brown: So you would do a liver function test as a routine thing I guess, but would you would evaluate the gallbladder with imaging such as ultrasound?

Dr. Bray: Well, I would think about it. I would want to know more about her family history and whether she’s had abdominal pain, particularly after meals with a lot of fat. The next steps would depend on my evaluation of the woman, but I would certainly consider these tests. Liver function tests if abnormal can be helpful, but they aren’t sufficient. Ultrasound of her gallbladder might be considered.

Dr. Brown: What other medical diseases may already be present?

Dr. Bays: According to the 2013 American Society of Bariatric Physician Obesity Algorithm, the potential adverse “disease” consequences of patients with increased body fat falls into 2 categories. The first is sometimes referred to as “sick fat disease” (adiposopathy), wherein anatomically, patients with increased body fat may have adipocyte hypertrophy and visceral fat accumulation,

leading to adipose tissue dysfunction (ie, endocrinopathies and immunopathies), which in turn contribute to some of the most common diseases encountered in clinical practice (eg, type 2 diabetes mellitus, hypertension, dyslipidemia). A second category is “fat mass disease,” which includes disorders most attributable to abnormal physical forces induced by excessive body weight (eg, musculoskeletal disorders, sleep apnea). Regarding evaluation, you already have provided much of what needs to be known, with respect to BMI, waist circumference, blood pressure as well as lipid and glucose levels. The increase in liver enzymes is expected, as fatty liver is a common finding in these types of patients. Although the fasting glucose of 105 mg/dL is in the prediabetes mellitus range, you might also consider obtaining a hemoglobin A1c blood level. This is because some patients with fasting glucose levels not in the diabetes mellitus range may have elevated hemoglobin A1c levels in the range diagnostic for diabetes mellitus, particularly if they have clinically significant postprandial hyperglycemia. Other potential diagnostic testing would be dependent on the clinical presentation, such as evaluation for secondary causes such as hypercortisolism and hypothyroidism. Sex hormone testing may be appropriate for hyperandrogenemia in women and hypoandrogenemia in men. Vitamin D levels may also be appropriate, as vitamin D deficiency is common among overweight and obese patients. Other diagnostic measures to consider, depending on the presentation, include cardiac testing, sleep studies, and C-reactive protein. Finally, many obesity specialists and their patients find value in body composition tests.^{2,3}

Dr. Brown: Therapy logically starts with dietary change. What types of dietary advice are practical and effective when given by the physician in the limited time of an office visit?

Dr. Bray: From a dietary perspective, you’d want information about meal frequency and timing. Many people have a tendency to eat very large meals late in the day. If you can get them to change some of these meal patterns, it may give you a way to help them even out their food intake. I have a particular concern about beverage intake particularly sugar-sweetened beverages that have a lot of calories in them. I think this is an important because that’s something people might change. The kinds of foods people eat and the way in which they prepare them—and whether the woman has a family she cooks for because that is going to influence the kinds of changes she can easily make. This information would give me a framework for helping her with the types of changes she might be able to make.

Dr. Brown: Modern medicine is in a flurry of genetic studies and related information and is attempting to apply this to many diseases. Are there any findings in the clinic that might make you think of genetic tests?

Dr. Bays: Not routinely. Not at her age.

Dr. Bray: I think the genetic issues are of concern mostly in childhood and adolescence. Once you get to be 55, there clearly is a polygenetic variability that is influencing how she responds to her diet. There is a fascinating

study on weight gain over 4 years in relation to sugar-sweetened beverage intake as a function of the number of genes that relate to obesity. If you were in the lower quartile for genes for obesity you didn't gain any weight over the 4 years. In the other 3 quartiles of risk genes, there was a graded increase in your weight gain for each beverage intake. Thus genetics clearly influence our response to the beverages we drink and the diets we eat. There are more than 50 genes related to obesity, but altogether, they account for about 5% of the variability in BMI. Nonetheless, they're important contributors to whether an individual becomes overweight.

Dr. Bays: Where genetics may have clinical application in adults is with respect to race. Different races have different genetic susceptibilities to developing metabolic disease. Those of Asian descent often have only a modest increase of body weight, but much higher risk for metabolic diseases and elevated cardiovascular disease risk with modest weight gain. So this would be an example of a genetic predisposition that would accentuate the adverse metabolic consequences of increased body fat.

Dr. Bray: Ethnicity might be a better word for these features. We've included South Asians, Chinese, and Japanese, all of whom have a much greater risk for metabolic syndrome largely associated with an increased visceral and ectopic fat relative to total fat mass. Also, fat distribution becomes important in the normal and overweight BMI ranges, but with a BMI of 40, fat distribution probably disappears as a variable of interest. Our patient has a BMI of 40 and her waist circumference would almost surely be above normal.

Dr. Bays: In support of considering genetics is that the waist circumference measurement criteria definitions for metabolic syndrome vary with regard to different races.

Dr. Brown: Is there a practical use for waist circumference in the general practitioner's office? There are different ways of measuring waist size and this measure has been criticized because it is done inconsistently. The community based studies usually report data from a standardized methodology.

Dr. Bays: Within the context of clinical trials, not only do we have training and standard operating procedures on how waist circumference is to be measured, but we also prefer to have the same individual performing waist circumference for the same patient. Because although the initial waist circumference value is important, what is sometimes as important are the changes in measurement after implementing weight loss interventions. Finally, once a BMI gets above 35 kg/m^2 , the value of a waist circumference is unclear.

Dr. Bray: I agree with you that the waist circumference is not very valuable in individuals with high BMI. And I would go 1 step further, the BMI, the waist circumference, and the weight to height ratio all have very similar correlations with cardiovascular risk factors, and provide little difference in predicting of outcome events for blood pressure or diabetes. From a clinical perspective, the waist circumference can give some additional information compared

with the BMI. One advantage of the BMI is that we have much more epidemiological data focused around the BMI across cultures than we have about weight circumference, which is much more culturally specific. So I would encourage us to stick with BMI and not add a waist circumference measurements of body fat because they're age-dependent, gender-dependent, and have other confounding issues. This is the same advice that the recently published Guidelines for Adult Obesity recommended in their report published in *Circulation* in October 2013. So I would stick with the BMI simply because there is so much more information behind it.

Dr. Bays: In support of this approach, within the clinical trial setting it is common to use BMI of greater than or equal to 30 kg/m^2 as a surrogate for a high waist circumference that would meet the criteria of the metabolic syndrome.

Dr. Brown: There seem to be these important ethnic differences in the distribution of adipose tissue. BMI measures may have different implications in different groups. In patients with South Asian ancestry, you see these relatively thin people with pot bellies. Is it in this group that waist measurement might be useful?

Dr. Bays: You are correct. As noted before, different waist circumference cutoff points can exist for different races. For example, with regard to Asian men the waist circumference measurement criteria is $\geq 90 \text{ cm}$ (35 inches), whereas for Asian women, it is $\geq 80 \text{ cm}$ (32 inches). This contrasts to the $\geq 102 \text{ cm}$ (40 inches) and $\geq 88 \text{ cm}$ (35 inches), respectively, for most of the non-Asian US population.

Dr. Bray: Regardless of ethnicity, you can do a number of things that will reduce the risk of developing diabetes. The Indian diabetes study, for example, took people who were prediabetic and induced a remarkable reduction in their risk for diabetes with a program of exercise and diet, but without much weight loss. It is by varying diet and becoming more physically active that you get the most benefit. The benefit of weight loss is best demonstrated in the American Diabetes Prevention Program where a mean weight reduction over 2.8 years of 5.5% produced a 58% reduction in the risk of developing diabetes. The Finnish Diabetes Prevention Program and the Indian diabetes program used exercise and the change in diet composition as their main strategies in reducing risk of developing diabetes.

Dr. Brown: Sometimes exercise may not reduce weight but results in replacing fat with muscle, which can accomplish the metabolic change we are seeking?

Dr. Bray: Exercise may be particularly helpful in maintaining muscle mass in younger people. In older people it may not do that. Sarcopenia is a major issue in older people. A high BMI in this group may reflect more fat and less muscle, and it may be a challenge to assess this unless you use more sophisticated techniques such as dual x-ray absorptiometry.

Dr. Bays: The degree of target weight loss in patients with overweight or obesity is dependent on the severity of their presentation as well as the degree you anticipate

weight loss might reasonably treat or prevent “sick fat disease” or “fat mass disease.” Given the well-established “obesity paradox,” which I hope we will discuss later, it is my sense that among the greatest health benefits of weight reduction in overweight and obese patients is the prevention of metabolic and fat mass diseases. This would be in contrast to patients with end-stage adiposopathy, characterized by longstanding diabetes mellitus, hypertension, dyslipidemia, advanced cardiovascular disease, and other irreversible end-organ damage. With the possible exception of bariatric surgery data, I am not sure the literature strongly supports modest weight reduction as being markedly beneficial in reducing overall mortality when weight loss intervention is delayed for too long.

Dr. Bray: My criteria for looking at desirable weight loss are influenced by the Diabetes Prevention Program in which they could plot the weight loss and the impact it had on developing diabetes. It’s a very nice smooth curve. If you have a weight loss of about 3%, you’ll reduce the risk of getting diabetes about 50% over a 3-year period of the trial. If you lose 10%, you’ll reduce your risk by 90%.

Small steps taken 1 at a time that rewards as you go along are much better because you can get considerable benefit even in a person with a BMI of 40 with a modest weight loss in terms of most of the metabolic changes.

Dr. Bays: I want to follow-up on that because when you look at the markers of adipocyte and adipose tissue functionality, you often find that a 5% to 10% weight loss can substantially improve the functionality of adipocytes and adipose tissue. It is also a 5% to 10% of weight loss that may afford substantial improvement in many of the metabolic diseases we have previously discussed.

Dr. Brown: I can remember Mayer Davidson 30 years ago say, it’s not a matter of getting skinny, it’s a matter of adjusting your risk factors, getting that 5-lb, 10-lb weight reduction that can be sustained, that’s most important.

Let’s say the patient has changed eating habits and adopted an exercise program and loses 5 lb. However, weight loss stops there. What would be your threshold for beginning drug therapy in such a patient?

Dr. Bray: Well, I think 1 lesson that came out of the 2 large trials in the United States, the Diabetes Prevention Program and the Look AHEAD trial, which we can apply here. We thought that in patients who already had diabetes, it would be more difficult to get them to lose weight. So we took a somewhat more aggressive approach with them. We began using meal replacements, a defined portion control intake. We gave them a regular weight loss program and we put a toolbox together to help them get a lot of additional help if they needed it. By adding the meal replacements and getting people to attend their sessions the participants were able to achieve an average 8.5% weight loss. This was 1.5% greater than we had seen in the Diabetes Prevention Program, which did not use meal replacements. So I would want to make sure that this woman had taken advantage of available replacements to use at home as a way of getting her food portion sizes under her

control. You also want to make sure that she begins a reasonable exercise program, done with enough frequency. The buddy system is a great help with starting and sustaining this. If you get someone in your office practice or 1 of her friends who has the same kind of problem to walk with her, you’re much more likely to get them both walking than her to walking alone. I think there are some things I would want to make sure that practical approaches to lifestyle issues were adequately tried before turning to medications.

Dr. Bays: What I might add is that first and foremost, whatever kind of nutritional intervention, it should be fewer calories than she previously consumed. Different nutritional interventions may be best for different individuals, depending on their clinical presentation, and which is most feasible. Philosophically, the 2013 Clinical Practice Guidelines for Healthy Eating by the American Association of Clinical Endocrinologists, the American College of Endocrinology, and The Obesity Society specifically note that because the primary disturbances in adipose tissue anatomy and function are etiologic in the development of metabolic derangements, a major focus of nutrition counseling for overweight or obesity is to correct adiposopathy. These guidelines even recognize the potential use of very low-calorie diets (<800 kcal/day) when administered by trained providers engaged in medical monitoring, as part of a high-intensity lifestyle intervention.

But for the general clinician, and especially for lipidologists, after addressing caloric quantity, I believe the most practical next step is for the clinician and patient to consider caloric quality. Specifically, if a patient with overweight or obesity has a metabolic profile of hyperglycemia, hypertriglyceridemia, and reduced high-density lipoprotein cholesterol levels, then low-carbohydrate nutritional intervention may have the greatest potential to address multiple metabolic parameters. Such an approach would be consistent with the 2013 Obesity, Adiposity and Dyslipidemia consensus statement from the National Lipid Association, the 2013 Clinical Practice Guidelines for Healthy Eating recommended by the American Association of Clinical Endocrinologists, the American College of Endocrinology, and The Obesity Society, and consistent with the American Society of Bariatric Physician Obesity Algorithm.^{2,4} Having said this, what may be most important for weight loss and especially maintenance of weight loss is what the patient willing and able to do. The 2013 American Heart Association/American College of Cardiology/The Obesity Society Guideline for the Management of Overweight and Obesity in Adults suggest that whatever reasonable, evidenced-based calorie-restricted diet is recommended, it should be based on the patient’s preference, health status, and preferably accompanied by counseling.⁵ This same sort of approach also applies to routine physical exercise. Sustaining the increased physical activity is also a major factor determining weight loss maintenance.

Dr. Brown: Any other thoughts about how to succeed with diet and lifestyle therapy?

Dr. Bray: Sugar-sweetened beverages and the large group of so-called fruit drinks and fruit juices, provide about 10% sugar. Except for the fruit juices, they have essentially no other nutrients. Fruit-drink is really a misnomer. They usually have less than 15% fruit juice and sometimes that juice is only the concentrate, which is really another name for sugar. This group is 1 kind of calorie that you can replace and I would encourage people to use carbonated beverages with lemon or artificial sweeteners or a variety low-calorie or calorie-free beverages to replace sugar-sweetened beverages because they are basically empty calories. The same thing is true for fruit juices; you have to use several oranges to get 1 glass of orange juice. How many people eat 3, 4, or 5 oranges in a day? The same thing is true for apples and apple juice. It takes several apples to make a glass of apple juice. With the apple you also get fiber and micronutrients. How many people eat 3 or 4 apples a day? I would thus spend some time working with her on the kinds of things she eats, and the kinds of things she drinks in order to help her get rid of some of those empty calories.

Dr. Bays: Another intervention is behavior modification. Behavior modification is often considered mysterious, with techniques perceived as only appropriately implemented by those specifically trained in psychology/psychiatry. The same applies with regard to nutritional interventions as recommended by a dietitian. It is not feasible for every patient who is obese to be seen by a psychological specialist or nutritionist; therefore, it is incumbent on clinicians to be aware of how to implement basic lifestyle measures. From a behavior therapy standpoint, some principles that may be practical and helpful include frequent encounters with medical professionals, education on the health importance of weight reduction as well as recommendations directed at stimulus control and goal setting. Another technique emphasized in recent years is cognitive restructuring, wherein helpful thoughts are recommended to replace unhelpful thoughts and thinking that lead to unfavorable eating behaviors. A few other techniques include behavioral contracting, wherein rewards are specified for achievement of incremental and simple goals, as well as problem-solving with contingency plans during times when there are setbacks. Perhaps most of all, self-monitoring and accountability via daily body weights, food diaries, and exercise records are simple, but important behavior modification tools often used for patients who are overweight or obese.

Dr. Brown: Do we have evidence that most moderately obese people, following guidance from a physician, will actually adhere to a self-monitoring program?

Dr. Bray: The Look AHEAD trial again gives us some insight into the question you are asking: what does it take to be successful with some of these behavioral strategies? They looked at the weight loss over 1 year, which is a reasonable period of time, and that is the time frame that I would discuss with this woman for her initial therapeutic plan. In terms of successful weight loss, the more meal

replacements a participant used, the more weight loss they got. It was a very graded response. The more often they came to the group sessions, the more successful they were in losing weight. Group sessions can be run by physicians or better yet by skilled office personnel. The third variable for successful weight loss was physical activity. The more times the participants reported exercising, the more weight they lost over the first 4 years. The other intriguing observation from this trial is that if you take the people who lose a lot of weight, that's more than 10% in the first year, there is a remarkable spread in how successful they are. About 40% of the group who lost 10% actually maintained that weight loss at 4 years, but the remaining 60% were scattered over the remainder of the weight loss spectrum, with some of them actually going back above where they started. We don't know what makes the difference between those who are very successful over 4 years and those who regain weight. This says that early success predicts higher probability that they will sustain the weight loss. Getting there quickly is better than not getting them there quickly.

Dr. Brown: If you're a primary care physician and you have done your best with the type of instructions, you both have discussed what would trigger you to refer your patient to some professional organization such as Weight Watchers?

Dr. Bray: If I didn't have a professional staff with experience in this effort, that's probably what I would do first. Weight Watchers has a very good and consistent track record. They do well in almost every setting. They consistently come up at the top or near the top of commercial weight loss programs. So I would do that first. If you're in the Kaiser Permanente System or some other large group practice where you can have someone dedicated to working with groups of people with unhealthy weight from several physicians, I would make use of that service. But if you don't have that, you could refer patients to Weight Watchers or some other commercial group. Alternatively, the Diabetes Prevention Program model is being implemented in many YMCA groups around the country you could determine if that program was available to you in your YMCA or YWCA group. That would provide a second referral strategy.

Dr. Brown: In the past year or so, there have been reports of telemedicine monitoring and support systems achieving rather remarkable results with significant and sustained weight loss. How practical are those methods? Can they be translated into general practice or does it require a highly trained and professional base of operations in an expensive setup to really support these?

Dr. Bays: Although hopeful, I would be cautious about these web-based approaches. Sure, it would be great if patients with overweight or obesity could effectively lose weight simply by logging into a website. But I have reviewed a number of clinical trial submissions of web-based weight management programs, with some negative reports not being published. Based on this anecdotal experience, it is possible that some degree of publication bias exists wherein the web-based systems that report favorable outcomes are more likely

to be published than those without success. But even among published web-based weight loss studies reporting benefits, the effects on body weight, waist circumference, and health outcomes are variable and perhaps less effective than face-to-face intervention.

The bottom-line for me is that, similar to nutritional and physical activity interventions (or basically any weight management intervention), web-based interventions are best when they are validated by science, and implemented based upon what works best for the patient.

Dr. Bray: Your point is well taken. Although we don't have quite enough information, we do have at least 3 good randomized control trials of 2 years' duration in primary care settings where primary care doctors randomized patients to 1 of 2 or 3 different settings. The trial done at Johns Hopkins is one of the best. That team was able to get and maintain a weight loss of more than 5% out to 2 years with 2 strategies. One of them was a phone call-based strategy, and the other was an Internet-based strategy. These 2 did much better than their control group assisted by an information newsletter. There was a second randomized controlled trial from the University of Pennsylvania that again used primary care physicians and a set of computer-based programs with support via telemedicine, but the results were not quite as good as the other trial. A third trial that focused on exercise as the primary treatment using counselors who were exercise specialists did not do as well. These patients only achieved about a 3% weight loss in their randomized primary care offices.

These trials point out that diet, as you were suggesting, Dr. Bays, is clearly an essential element of any weight loss program. You can support the effectiveness of the diet with some of these telemedicine methods. The studies from Johns Hopkins and the University of Pennsylvania were sufficient to convince the Center for Medicare and Medicaid Services to fund primary care physicians if they managed to meet specific weight loss criteria over the first year of treatment. However, I am concerned about a woman with a body mass index of 40; that's pretty high for most of these trials. She is in a group for which there are few randomized clinical trials of weight loss.

Dr. Brown: From a practical business point of view, will you get compensated? As a practicing physician such as a general internist, there is difficulty in making the needed income to support an adequately staffed and equipped office. I am concerned that many are not going to be willing to take on additional activities that don't provide support to their staff or to their own wellbeing. Have we reached a point where these procedures are practical in this sense?

Dr. Bray: For some doctors in appropriate practice settings, I think the tools are available to implement lifestyle changes for their patients. However, this is not for most primary care physicians, but I think those who have an interest in the problem of unhealthy weight and what is called behavioral medicine may find it worthwhile and will effectively organize how they deliver these services. If they're part of a group with enough staff and patient flow, it is

more feasible to do it efficiently, particularly when they can have staff well trained in delivering lifestyle messages. If they can deliver weight loss, they will get reimbursed according to Center for Medicare and Medicaid Services criteria. The recent Guidelines for the Management of Obesity in Adults provide strong support for the use of lifestyle in managing obesity and unhealthy weight.

Dr. Bays: Establishing an interest, building an infrastructure, and doing so toward the targeted care of patients who are overweight or obese may be the most cost-effective approach. For example, endocrinologists have interest and infrastructure toward management of diabetes mellitus patients, which may include implementation of insulin and other diabetes mellitus injectables, achievement of diabetes mellitus medical metrics, and diabetes mellitus education through diabetes educators and/or specialized nurse practitioners. Similarly, bariatric specialists who focus their medical practices on management of patients who are overweight and obese can have economies of scale, which may allow for the kind of ancillary support required and that may not otherwise be feasible in a general medical practice.

Dr. Bray: As you know there is now an American Board of Obesity Medicine, which is a joint effort of several societies, headed by The Obesity Society, which certified more than 100 people last year. So we're beginning to see a number of people who have the broad base of credentials that give them the knowledge base and the technical base to manage obesity effectively.

Dr. Brown: Maybe they will set the standards but it is such a huge problem affecting millions of people. To be successful, we must have many thousands of doctors involved; not just a few hundred.

Dr. Bays: Wouldn't you say the analogy is very similar to the National Lipid Association?

Dr. Brown: Yes.

Dr. Bays: But not every lipid abnormality can be treated by a lipid specialist, right?

Dr. Brown: Absolutely right. That's why the National Lipid Association has been so oriented to all physicians, especially primary care physician as well as nurses and other health professionals.

I would like to now turn to the application of drug therapy in the obese patients. We have new agents recently approved by the US Food and Drug Administration (FDA) specifically for weight loss. When would you consider drug therapy in the patient whose lifestyle changes have been inadequate to address the potential for serious medical outcomes?

Dr. Bray: I would have a very low threshold for the use of metformin in this woman with a fasting plasma glucose of 105. Metformin is a very safe drug if the patient can tolerate it. I would be inclined to put this person on metformin. And if she takes a peak dose of around 1500 mg/day, the 10-year data from the Diabetes Prevention Program suggest that she would maintain almost a 4% weight loss.

Dr. Brown: Is it because of the appetite-suppressing effect?

Dr. Bray: How metformin works is not entirely clear. It may affect the AMPK system, which is an intracellular energy-sensing system. However it works, it clearly has a long-term effect with very low side effects, so the practical concern in its use is that the patient may not tolerate the gastrointestinal side effects.

Dr. Bays: I agree that weight management pharmacotherapy should be a consideration. I believe the decision as to which agent is the most appropriate should be based on the agent that might be expected to be the safest, most tolerated, and effective for the individual patient. Regarding approved use, I believe the FDA has done clinicians and patients a favor, because labeling of weight management pharmaceuticals requires a 12-week assessment period. If after 12 weeks, the weight management agent has not helped achieve the desired or anticipated effectiveness, then a decision should be made to stop the weight management agent, or in some cases, perhaps increase the dose of the weight management agent. This approach may mitigate the all-too-common situation wherein prescriptions of ineffective drugs simply get refilled, without evidence that they are affording benefits to patients.

Dr. Bray: That's right.

Dr. Brown: How do you deal with the problem of failure of a drug to perform? If patients are disappointed in the weight reduction they stop the drug, they may also view the physician as not being successful and therefore stop the doctor visits. Can you prepare the patient for failure when you prescribe that first drug?

Dr. Bays: Well, to your point, let's go to clinical trial data. When patients who are overweight or obese enter into clinical trials of weight management pharmacotherapies, they may receive clinical management, nutritional and physical activity guidance, behavior modification, laboratory, pharmacotherapy, and interactions with clinicians and research nurses—all free of charge. In fact they often are reimbursed for time and travel. Yet at the end of 1 year, the dropout rate is as much as 50%, which goes straight to your point. Because even under what might be considered very favorable circumstances, maintenance of weight management care is often challenging. I believe this can be explained at least partially by the failure to achieve weight loss expectations that are unrealistic.

Dr. Bray: I come back again to the 2 clinical trials I have already discussed. Both the Diabetes Prevention Program and Look AHEAD trials maintain a 90 plus percent follow-up rate out to 10 years. This is truly remarkable. No drug trial does better than 80% and few do that well in retaining patients. The Pounds Lost trial had an 80% follow-up at 2 years but that's exceptionally good. Most drug trials are in the range of 50% to 60% dropout first year. One of the things we need to learn more about is how do you get people to adhere to the programs they go on? Weight loss drugs are particularly challenging, first, because you usually define a goal at the beginning, and it's almost always larger than you could possibly achieve. So if you lose weight and let's say this woman lost 10%,

which would be 4 BMI units, that would be clinically very effective, but it would still leave her weighing 230 pounds. And she's going to achieve a plateau sometime around 6 months of therapy with whatever you do for her, surgery included. And at that point she's going to ask herself, well I paid \$200 a month or more for the medications I'm getting, I'm also paying the doctor for the therapy I'm getting, and I'm not losing any more weight, and I'm still 80 lb above where I want to be. Why am I paying this \$200 a month? Am I really getting anything out of it? I've probably got all I'm going to get and maybe I'm as "cured" as I'm going to be. She is now frustrated with the doctor because he or she can't do more, and with the medication because it doesn't do more. I think that's a major challenge that every physician must feel as he or she implements a weight management program with medications.

Dr. Bays: Perhaps 1 of the ways of meeting this challenge is an evolution in our thinking about our treatment goals. For patients with fat mass disease, clearly losing fat mass is a priority. However, for many other patients who have "sick fat disease" or adiposopathy, the focus is not just on the weight of the patient, but also on the health of the patient. From a practical standpoint, describing to patients how fat weight gain may be causing their body fat to become "sick," and how fat weight loss may help their body fat to become more "healthy," might be a more effective approach than a detailed discussion of the diagnostic criteria of the metabolic syndrome. So framing the increase in body fat in the context of a "disease" makes a lot of sense.

Dr. Bray: Again, the Look AHEAD trial has an interesting analysis of your 4-year weight loss and the pattern of loss at the beginning of the trial. It is very clear that the more weight you can lose in the first 3 months, the more weight loss you will have at 4 years. What this suggests to me is that when you first see a patient and put a weight management plan in place, you ought to make it as "vigorous" as you can.

Dr. Bays: In support of Dr. Bray's point is a 2013 publication in the *New England Journal of Medicine* wherein various obesity myths are discussed. One of the 7 listed "myths" was that "large, rapid weight loss is associated with poorer long-term weight outcomes than is slow, gradual weight loss."⁶

Dr. Bray: I would conclude the opposite based on the Look AHEAD study. With a study group of 2500 people in each group, it's not a small trial, and it shows that more rapid initial weight loss is associated with better long-term weight maintenance.

Dr. Brown: I would now like to discuss the choice of drugs that are specifically approved for weight loss. What would be the factors that would cause you to choose 1 versus another? In the case of poor response with the first, what would be your second-, third-, and fourth-line drug?

Dr. Bays: Currently, phentermine is the most widely used weight management pharmaceutical, probably because it was approved for clinical use in the 1950s, and

because it is generic. Orlistat remains available, but is not a widely prescribed weight management agent, largely because of its adverse experience of fatty, loose stools and fecal incontinence. These problems are directly attributable to its mechanism of action as a gastrointestinal lipase inhibitor. Having said this, I have found orlistat very appropriate for selected patients. For example, I had a patient who was obese with spinal fracture and chronic constipation. He also had type 2 diabetes mellitus, hypertension, and dyslipidemia. Not only was orlistat effective with weight reduction and improvement in metabolic parameters, but it also improved his bowel function. So I think of orlistat as a specialty drug that is nice to have available for selected patients.

Dr. Bray: Beside weight loss, orlistat has an additional effect on serum cholesterol. The drug results in a pool of undigested triglyceride in the bowel, which acts as a sink for cholesterol. So if you have elevated cholesterol, as this woman does, that is an additional consideration in choosing orlistat.

Dr. Bays: Dr. Bray is correct. In the National Lipid Association consensus statement: "Obesity, adiposity, and dyslipidemia," we make that precise point. In working exclusively in the gastrointestinal tract, it differs from other weight management agents that predominantly work through the central nervous system.

Dr. Brown: Orlistat reduces caloric intake physically, whereas phentermine suppresses appetite and reduces intake by that mechanism. Should we be mixing those 2? Is that an effective and safe combination?

Dr. Bray: Orlistat was tried with sibutramine, and there was no additional weight loss. Thus, the combination didn't make any difference. Therefore, I wouldn't recommend combining it with any existing drugs. There are no data supporting a benefit from prescribing another drug with orlistat in combination. But orlistat added to sibutramine, a drug that is no longer marketed, didn't have any additive effect.

Dr. Bays: Regarding alternatives to orlistat and phentermine, lorcaserin is a 5-HT_{2C} receptor agonist approved for weight management, which via its interaction with the central nervous system feeding center (arcuate nucleus of the hypothalamus), increases satiety. Clinical trial data indicate that in patients with overweight or obesity, lorcaserin has modestly favorable effects on the lipid profile and blood pressure, but substantial effects on glucose levels in patients with type 2 diabetes mellitus. A drop in hemoglobin A1c of 0.5% compared with placebo has been reported. That is in the range you might expect from an anti-diabetes mellitus drug.

Dr. Brown: Was the reduction in hemoglobin A1c correlated with the weight loss?

Dr. Bays: Yes.

Dr. Brown: What about adverse effects attributable to the drugs you have mentioned?

Dr. Bray: Before you get to adverse effects, let me make 2 comments. First, this woman is 55, so she's probably

postmenopausal which would make topiramate a perfectly acceptable drug without pregnancy tests. I would put this woman on the middle dose of the combination of phentermine and topiramate, because I think she would get the maximum weight loss with that combination in the first 3 months. The 2-year clinical trial data, among completers, showed that they still maintained nearly 10% weight loss. That's very impressive weight loss. So that would be my first choice for this particular patient.

Dr. Brown: You would not add metformin to this?

Dr. Bray: Yes, I probably would use metformin and a combination of phentermine/topiramate together.

Dr. Brown: And what adverse effects would you be looking for?

Dr. Bray: Well, there are a variety of potential adverse effects with these drugs. With the combination of phentermine/topiramate and fewer side effects with lorcaserin; one major issue with phentermine/topiramate is concern about pregnancy. You have the usual effects of associated weight loss drugs, insomnia, and constipation, but I think the 2 that are noteworthy are paresthesias and a drop in bicarbonate with mild metabolic acidosis because topiramate is a carbonic anhydrase inhibitor. It's usually not clinically significant but it can be. The third issue is memory issues. This problem derailed topiramate as a single medication for weight loss. Phentermine may overcome some of the behavioral effects of topiramate, although that is not clear from the literature because it hasn't been systematically tested. But the package insert cautions about the issue of memory and behavioral issues. So I think the physician needs to warn his or her patients about these potential side effects. Having said all of this, I would probably start this particular woman on phentermine/topiramate in the extended-release form.

Dr. Brown: Okay. Is there another approach if this drug combination didn't produce the effect you want?

Dr. Bray: Because this woman is a borderline diabetic, there are a number of antidiabetic drugs that might be considered for her. I have already mentioned metformin. If she were diabetic, exenatide, pramlintide, liraglutide, or a gliflozin could be considered. They all produce weight loss and are approved by the FDA for treating diabetes. Combining phentermine, which is approved for obesity, with pramlintide, which is approved for diabetes, produces a 10% weight loss in diabetic patients. Pramlintide is an injectable drug, whereas phentermine is given orally. Because this woman is a borderline diabetic, liraglutide might be a reasonable choice. Both exenatide and liraglutide have or will have long-acting formulations approved by the FDA.

Dr. Bays: The metabolic effects of weight management with pharmacotherapies are promising, such as those with the phentermine/topiramate combination and the lorcaserin. But the effects of other concurrent therapies matter as well. Agents often associated with weight loss include some antidiabetes agents, as described by Dr. Bray (eg, metformin, glucagon-like peptide-1 agonists, sodium glucose co-transporter inhibitors) as well as neurological

agents such as topiramate and bupropion. Currently, these not FDA-approved for weight loss. Conversely, other agents are often associated with weight gain, and include steroids (eg, glucocorticoids, estrogens, tamoxifen, progestins), some diabetes therapies (some insulins, sulfonylureas, thiazolidinediones), some highly active antiretroviral protease inhibitors, some beta-blockers, some antihistamines (eg, diphenhydramine), some chemotherapies, and a number of antidepressant, anti-seizure, and psychotropic agents. So, part of the therapy should be considering reducing or substituting other agents for the latter group if possible.

Dr. Brown: So, it sounds like we would want consider discontinuing such drugs after our initial evaluation before we began treatment.

Dr. Bray: I would agree. Depression would be a clear problem that I'd want to know about because there are antidepressant drugs that appear to induce weight gain and others that produce weight loss. Thus the physician has the opportunity of getting someone off a weight gain drug and to begin one for the same condition—depression—that's weight neutral if not 1 that produces weight loss.

For the patient who has migraine headaches, topiramate is an approved drug that also produces weight loss.

Dr. Bays: That's the point. We now have approved treatments for a number of conditions that may have better body weight effects. For diabetes mellitus management, for example, many endocrinologists and primary clinicians alike often prefer metformin or glucagon-like peptide-1 agonists over insulin or sulfonylurea.

Dr. Bray: Pramlintide combined with phentermine produces significant weight loss.

Dr. Bays: Exactly.

Dr. Brown: Are there any other oral agents that we should discuss?

Dr. Bray: Lorcaserin is a potentially useful drug. When you prescribe this drug, you need to evaluate the patient at 3 months for 5% weight loss. If it is less than 5%, consider other strategies. However, some patients will respond very well to this medication. It is difficult to predict who will respond and who will not. Evaluating the initial rate of weight loss is a good criterion for all medications. If patients haven't lost 5% or more at 3 months, it's time to take a careful look at the treatment strategy. There's clearly variability in response to all drugs. Although lorcaserin didn't meet the FDA's criteria 1 for a weight loss of 5% more than placebo, there were nonetheless many patients with much more weight loss than 5%. Thus, evaluating the response of the individual patient to drugs and selecting the ones who respond very nicely to lorcaserin is a good strategy. There will be some who won't respond at all. There will be some who respond very well to metformin; there will be some who can't take it and need an alternative approach.

Dr. Brown: So, the testing of responses in a given patient is extremely important. It would seem that it would

be important to tell patients that there is a significant variability of response before beginning a weight loss drug. The reassurance that there are several choices might be helpful in patient compliance?

Let's assume that we have applied the therapeutic maneuvers outlined before in our patient. After a year, she has lost 26 lb (10% of her baseline weight) but her BMI is still 36. Is she an appropriate candidate for bariatric surgery? What would be your considerations in terms of making that decision?

Dr. Bray: She has a BMI of 36 with "comorbidities" and is thus an appropriate candidate. The evidence convinces me that our current body mass index criterion of 40 or more without comorbidities may be the wrong one. Now this woman had impaired fasting glucose, so she's prediabetic. With prediabetes, I would like her BMI below 35 and consider trying to reach 30. There's quite convincing data that you will improve the likelihood of reducing the risk of getting diabetes substantially if you do some form of bariatric surgery in patients whose BMI is in range of 30 to 35.

Dr. Bays: The 2013 American Heart Association/American College of Cardiology/The Obesity Society Guideline for the Management of Overweight and Obesity in Adults suggest that for individuals with a BMI <35 kg/m², insufficient evidence exists to recommend for or against bariatric surgical procedures.⁵ However, depending on the scientific organization, payer, and patient presentation, a body mass index of 30 kg/m² may be all that is required from a BMI standpoint for consideration of bariatric surgery. But to me, the real decision and to the choice of whether it be weight management pharmacotherapy or bariatric surgery, is not just how such interventions may improve the weight of patients, but also how they improve the health of patients.

In this case, the patient has the metabolic syndrome with an initial plasma glucose of 105 mg/dL. So she clearly has adiposopathic metabolic abnormalities that one might reasonably expect would improve with agents that promote weight loss. The question is when. Some studies suggest that when patients with overweight or obesity have end-stage obesity/adiposopathy, with advanced complications, the benefits of weight reduction at that point are unclear. But surely no one would disagree that early and aggressive intervention for the purpose of preventing the onset of metabolic disease is not without clinical benefit. So why wait? It seems unreasonable to wait until advanced and potentially irreversible longstanding diabetes mellitus, high blood pressure, dyslipidemia, cardiovascular disease, sleep apnea (etc) to then think about implementing aggressive weight loss measures.

Dr. Brown: With this set of risk factors and failure to lose sufficient weight to alter them significantly, you would consider her for bariatric surgery.

Dr. Bays: Yes.

Dr. Brown: Would you favor a particular surgical approach or should you leave that totally to the surgeon who perhaps would be an expert in 1 form of surgery?

Dr. Bray: What surgeon do you know that's going to take an internist's advice?

Dr. Bays: I think your point is a good one. The best potential for bariatric surgical success by a bariatric surgeon is a prior history of bariatric surgery success. That is why it is so important to get a sense about the surgeon and surgical program, in determining not just what bariatric surgery is potentially best, but also who might be the best one to do the surgery, and where such surgery is best performed.

Dr. Bray: I would send her to a facility that's a center of excellence in bariatric surgery because it's quite clear that surgeons who've done more of these operations do better with fewer complications. And you want to have a surgeon who's done at least 50 operations. When I talk to them privately, they say 100 or more gets your operative problems down to about as low a risk as you can get. So you want to have a center that does a lot of bariatric surgery and one that has follow-up for postoperative care. One thing surgeons don't do very well is postoperative follow-up. They like to operate so you need to have a structure for the surgeon that will provide for the patient's long-term follow-up. In my experience, most of the places that do a lot of these operations in fact do have that structure. They definitely follow the patients for a while.

Dr. Bays: Follow-up is key. As an endocrinologist, I do not see the patients with highly successful bariatric surgery. I selectively see the failures. I see the patients who did not have the kind of quality follow-up described by Dr. Bray, those who present years later with electrolyte disturbances, vitamin deficiencies, profound hyperparathyroidism, osteoporosis, neuropathies, and on and on. Based on advertisement, one might get the sense that bariatric surgery is a very common procedure. However, I believe this area is still somewhat in its infancy. And as this area matures, so shall implementation of patient quality control and quality assurance measures to better ensure appropriate follow-up. What patients need to completely understand is this is not a situation wherein the bariatric surgery is performed, and then the patients can safely be sent home to enjoy the uncomplicated weight loss. That is simply not medical reality.

Dr. Bray: Our understanding of bariatric surgery, as with our understanding of weight loss, is informed by these larger trials that have a lot of postsurgical patients. One of the best of these is the Swedish Obese Subjects Study, in part because it is managed by an internist, not a surgeon. And in the 2000 operated people in the Swedish Obese Subjects Study, they had 4 deaths. Professor Sjostrom told me a couple of times that to be able to see a positive benefit, even though lots of things occur early, you have to wait nearly 10 years to be able to see the advantages to the patients over the early disadvantages from death and the issues raised by Dr. Bays. Surgical mortality has been gradually reduced and is now between 0.1% and 0.5%, depending on the surgeon's experience, but it is still 2% to 4% where the experience is less extensive.

Dr. Bays: I believe it was you, Dr. Brown, as coauthor of the National Lipid Association 2013 Obesity, Adiposity and Dyslipidemia consensus statement, who recommended we include data from sentinel bariatric surgery studies. Because these studies not only support such surgically induced weight loss as improving lipid levels, but also as improving diabetes mellitus and other metabolic diseases—not to mention an improvement in cardiovascular risk and overall mortality.

Dr. Brown: I believe that the demonstration of long-term beneficial effects, over approximately 10 years, was very important to demonstrate.

Dr. Bays: That is correct.

Dr. Brown: And so what do we tell our patients when we decide to refer them to a surgeon? What do we warn them about and what are the things that they should know as a consumer?

Dr. Bays: Given the number of advertisements, it is often the case that patients approach their clinician for self-referral for bariatric surgery.

Irrespective of all the wonderful data in the literature and irrespective of the lofty expectations of patients with overweight and obesity, the clinician needs to have a frank conversation about how bariatric surgery is not a panacea. It is not a replacement for a lifelong commitment to appropriate nutrition and physical activity, behavior therapy techniques, and ongoing management of other medical conditions. As mentioned before, follow-up is critical.

Dr. Brown: And in this setting of bariatric surgery, is it important to maintain the medical therapy that may have been started with partial success. Will bariatric surgery patients often need to continue these drugs we talked about earlier?

Dr. Bray: As with all therapies for weight management, there's a phase of weight loss and then there's a plateau. And then for some of these patients, depending on the procedure, there is a weight regain—the laparoscopically placed bands being the most likely to be associated with significant regain. Before a surgeon redoes a Lap-Band procedure, most bariatric surgeons would prefer to see patients try some of the medications to slow the weight gain or prevent it. The gastric bypass and the gastric sleeve operations seem to be the best procedures in terms of stability of long-term body weight.

Dr. Bays: One of the aspects of bariatric surgery, especially with gastric bypass, gut hormone alterations may not only have an effect on weight reduction and maintenance of weight reduction, but gut hormone changes may also have an effect on improvements in the metabolic profile, perhaps independent of weight loss.

Dr. Brown: This is a fascinating area. It has become clear the intestine is a complex endocrine organ. Changing the structural functionality changes the endocrine functionality.

Dr. Bray: The adipose tissue, brain, and gut seem to be constantly talking to one another through chemical and neural signals. In addition studies of the intestinal microbiome is certain to change the way we view the gut again

because it's clearly responsive to the things we eat and probably to our genetic background. It may also contribute to why we get obesity.

Dr. Brown: This is truly fascinating. Is there research that may point to whole new ways of thinking about obesity and its therapy?

Dr. Bray: Indeed there is.

Dr. Bays: In just 1 example, PYY is a member of the pancreatic polypeptide family produced by the large bowel, and that is released postprandially into the circulation. Because prior animal studies suggested PYY markedly reduced inhibition of food intake, we were involved in clinical trials testing this potential mechanism. In a publication of the efficacy and safety of intranasal peptid YY3-36 for weight reduction in obese adults, patients had a high discontinuation rate because of nausea and vomiting. The reported results suggested: "no meaningful inference can be drawn from the few patients who completed the study," with a conclusion that "intranasal PYY (3-36) as administered at these intervention doses and preprandial timing is not efficacious in inducing weight loss in obese patients after 12 weeks of treatment."⁷ So this is an example in which we have attempted to exploit the gastrointestinal/central nervous system connection toward promotion of weight loss. Although this 1 example failed because of tolerability, it did validate the approach you suggested.

Dr. Bray: One issue for lipidologists is dietary fat. The high-fat diet and the lipids it contains seem to have an inflammatory effect on the bowel. And one of the issues that is becoming clearer and clearer is that that response, particularly to the higher fat diets that we eat makes the gut more permeable and that a lot of the inflammatory response we see in adipose tissue is probably a function of lipopolysaccharides being absorbed through the gut.

Dr. Brown: These are quite large molecules. Is there clear evidence that the normal intestine can absorb such structures?

Dr. Bray: Absolutely.

Dr. Brown: And do they increase the inflammatory behavior of the macrophage population?

Dr. Bray: Yes, that's exactly what they do because the Toll-like receptor 4 is the one on which they act. The other thing that's true in both man and animals is that a high-fat diet that has this effect on the gut and adipose tissue also produces inflammatory responses in the brain. And one hypothesis leptin resistance is that the brain may have learned in response to a high-fat diet to become resistant to leptin through inflammatory changes in the glial systems of the brain. There's a whole new concept around the relationship of our diet and the lipids it contains and inflammatory responses. I focus on lipids because they seem to be major players and what the gut does in response to diet. These new concepts of inflammatory responses open up a whole new horizon. There's a fascinating study that identified a drug that could block a component of the inflammatory system and prevent weight gain with high-fat diets. Thus my

model for obesity has changed dramatically over the past couple of years because of this inflammatory system and its effects. Lipids in our diet and gut have the gut on fat and brain independent of the nature of those tissues in the first place.

Dr. Bays: It is extraordinary that it took until 2013 for the general medical profession to (finally) acknowledge obesity as a "disease." But even today, we have skeptics. One of the reasons for skepticism is the obesity "paradox." Perhaps what is most paradoxical about the obesity paradox is that about 8 or more different obesity paradoxes exist.³ I think much of the misunderstanding is related to the lack of understanding of the degree by which clinicians appreciate adipocytes and adipose tissue as being active from an endocrine and immune standpoint. Dr. Bray's discussion takes it 1 step further, in that not only might a pathologic increase in body fat increase this risk for fat mass and sick fat disease (adiposopathy), but high fat intake might also have adverse central nervous system consequences.

Dr. Brown: Which then alters appetite control?

Dr. Bays: Possibly, at least in animal studies.

Dr. Bray: What high-fat diets do exactly is still being unraveled. The fact that high-fat diets in man and animals can produce "inflammatory" signaling in the brain and the body is a new frontier for potential therapeutic insights.

Dr. Brown: I want to thank Drs. Bray and Bays for answering my questions and for bringing a variety of important issues to our attention. This has been a blend of very practical information of use in the office practice of all physicians as well as a discussion of the directions new research may take us in the understanding and treatment of obesity. I know that the readership of this *Journal* will find this to be useful and inspiring.

References

1. Bays HE, Toth PP, Kris-Etherton PM, et al. Obesity, adiposity, and dyslipidemia: a consensus statement from the National Lipid Association. *J Clin Lipidol*. 2013;7:304–383.
2. Seger JC HD, Westman EC, Lindquist R, et al. American Society of Bariatric Physicians Obesity Algorithm: Adult Adiposity Evaluation and Treatment Version 20131. Available at: <http://www.obesityalgorithm.org>. Accessed December 31, 2014.
3. Bays HE. Adiposopathy is "sick fat" a cardiovascular disease? *J Am Coll Cardiol*. 2011;57:2461–2473.
4. Gonzalez-Campoy JM, St Jeor ST, Castorino K, et al. Clinical practice guidelines for healthy eating for the prevention and treatment of metabolic and endocrine diseases in adults: cosponsored by the American Association of Clinical Endocrinologists/the American College of Endocrinology and the Obesity Society: executive summary. *Endocr Pract*. 2013;19:875–887.
5. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society [e-pub ahead of print]. *J Am Coll Cardiol*. <http://dx.doi.org/10.1016/j.jacc.2013.11.004>, accessed February 21, 2014.
6. Casazza K, Fontaine KR, Astrup A, et al. Myths, presumptions, and facts about obesity. *New Engl J Med*. 2013;368:446–454.

7. Gantz I, Erond N, Mallick M, et al. Efficacy and safety of intranasal peptide YY3-36 for weight reduction in obese adults. *J Clin Endocrinol Metabol.* 2007;92:1754–1757.

Recommended reading

1. Bray GA. *A Guide to Obesity and the Metabolic Syndrome: Origins and Treatment.* New York: CRC Press: Taylor and Francis Group; 2011.

2. Bray GA, Ryan DH. Medical therapy for the patient with obesity. *Circulation.* 2012;125:1695–1703.

3. Bray GA. Energy and fructose from beverages sweetened with sugar or high-fructose corn syrup pose a health risk for some people. *Adv Nutr.* 2013;4:220–225.

4. Bray GA, Look M, Ryan DH. Treatment of the obese patient in primary care: targeting and meeting goals and expectations. *Postgrad Med.* 2013;125:67–77.

5. Gloy VL, Briel M, Bhatt DL, et al. Bariatric surgery versus non-surgical treatment for obesity: a systematic review and meta-analysis of randomised controlled trials [e-pub ahead of print]. *BMJ.* <http://dx.doi.org/10.1136/bmj.f5934>, accessed February 21, 2014.