a negative outcome (i.e., not favoring the intervention), two favored the intervention, and one, with a factorial design, had a mixed outcome. Given this performance, it is impossible to argue that Califf has a pro-industry bias. On top of this, for the past 3 years the vast majority of his funded salary came from leadership roles in the Clinical Translational Science Award from the National Institutes of Health (translational medicine), the NIH Collaboratory, the Patient-Centered Outcomes Research Network (large-scale population health research), and the Duke Center for Medicare and Medicaid Innovation (CMMI) project, which developed a model approach to health care disparities in diabetes, using geospatial mapping to deliver clinical care and social support more effectively.

Our association with Califf grows from a decade of mutual service on the Forum on Drug Discovery, Development, and Translation of the Institute of Medicine (now the National Academy of Medicine). Through this decade of service, Califf's primary interest was clearly in gathering and using solid information to promote the health and well-being of people suffering from disease. His aim was always to find better ways to diagnose and treat illness. He wanted well-gathered data on which to base all our clinical decisions and wanted to design and implement health systems that worked effectively to improve the outcomes of individuals and populations. Califf's experience, his proven leadership abilities, his record of robust research to guide clinical practice, and his unwavering dedication to improving patient outcomes are unsurpassed qualifications for the post of commissioner of the FDA; we strongly endorse his nomination and urge the Senate to act favorably on it.

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The Obesity Epidemic — Understanding the Disease and the Treatment

Caroline M. Apovian, M.D.

The prevalence of severe obesity in the United States has increased dramatically, not only among adults but also among children. The increase in childhood severe obesity, defined as 120% of the age-specific 95th percentile of body-mass index (BMI), has been alarming; the prevalence has risen from 4% during 1999–2004 to 6% during 2011–2012.[1,2]

Although the use of healthy lifestyle approaches to treat younger children with obesity

can successfully reduce BMI, the implementation of these approaches among adolescents and adults is much less effective.[3] Unfortunately, approximately 90% of children with severe obesity will become obese adults with a BMI (the weight in kilograms divided by the square of the height in meters) of 35 or higher. Marked obesity in children leads to earlier development of atherosclerosis and type 2 diabetes because of the coexistence of cardiometabolic risk factors associated with obesity.[4]

There is good evidence indicating that although obesity may start as a lifestyle-driven problem, it can rapidly lead to disturbed energy-balance regulation as a result of impaired hypothalamic signaling, which leads to a higher body-weight set point.[5] Thus, obesity may be considered a disease initiated by a complex interaction of genetics and the environment.

Although medication can help lower the body-weight set point in adults, none of the medications that have recently been approved for adult obesity, such as phentermine–topiramate, lorcaserin, naltrexone–bupropion, and liraglutide (3.0 mg), have been studied extensively in children and adolescents. In general, only orlistat (which has been approved by the Food and Drug Administration [FDA] for childhood obesity) and metformin are used in these age groups.[6] Exenatide, a glucagon-like peptide-1 (GLP-1) receptor agonist approved for type 2 diabetes, appears promising as a treatment for pediatric obesity, but it has not been approved by the FDA for this purpose.[7]

Most experts in childhood obesity focus on primary prevention rather than on the treatment of extant obesity, possibly because treatment may seem increasingly futile as obese children mature.[8] However, that calculus does not include bariatric surgery, which leads to sustained weight loss, thereby altering signaling to the hypothalamus and leading to physiological satiety, at least in part through changes in the secretion of gut hormones such as GLP-1.[9]

Assessing the benefits and risks of bariatric surgery in adolescents is challenging, because obesity is not invariably viewed as a disease and because many adolescents are less adherent than adults with regard to postoperative care and follow-up. In the United States, bariatric surgery in adolescents is performed only after an intensive screening process that includes the documentation of physiological maturation (puberty) and adequate psychological maturity.

In this issue of the *Journal*, Inge et al. report the long-term (3-year) results of the Teen-Longitudinal Assessment of Bariatric Surgery study (Teen-LABS), a multicenter prospective study of bariatric surgery in an adolescent population.[10] Surgery led to a mean total body-weight loss of 27% among participants, as well as to remission of type 2 diabetes in 95% of participants who had had the condition at baseline, of abnormal kidney function in 86%, of prediabetes in 76%, of hypertension in 74%, and of dyslipidemia in 66%. However, in their study, adverse events included ferritin deficiency in 57% and additional abdominal procedures in 13% of participants.

Does the Teen-LABS study inform therapeutic decision making for adolescents with severe obesity? Should a greater number of markedly obese teens undergo bariatric surgery, and at what point in their lives?

The prevention of severe obesity in adolescents is paramount, and bariatric surgery will not stop the progression of the disease. Continued efforts to work with government and the food industry to ensure that healthier food and increased physical activity are available for all children through communities, schools, and other avenues are important if the increase in severe obesity is to be halted. Because lifestyle interventions early in childhood may be effective, these should be instituted. But for adolescents with severe obesity for whom conservative medical treatment has failed, the present study indicates that surgery can result in substantial weight loss and resolution of coexisting conditions. Thus, it may be beneficial to consider such adolescents for bariatric surgery, before they reach adulthood, when some conditions become less reversible.

The management of obesity is difficult. Emerging evidence suggests that bariatric surgery may establish a new body-weight set point by altering the physiological mechanisms of body-weight regulation, thereby causing sustained weight loss. Continuing research may establish the biologic mechanisms through which bariatric surgery works and may uncover new nonsurgical options for the treatment of both adult and pediatric obesity. In the meantime, Inge et al. provide longer-term evidence that bariatric surgery can provide relief from the tremendous physical,

social, and psychological burden that severe obesity causes in a growing number of American youth. However, even longer-term (>10-year) follow-up will be necessary to track the persistence of the associated micronutrient deficiencies, as well as the emergence of other deficiencies and other unanticipated long-term complications. Only then will providers be fully informed for the counseling of adolescents and their families with regard to the benefits, risks, and timing of bariatric surgery.

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Chemotherapy for Tuberculous Meningitis

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Tuberculous meningitis, the most destructive form of tuberculosis, continues to be associated with considerable mortality and morbidity; among children, it is the major cause of death resulting from tuberculosis. The consequences of tuberculous meningitis are yet again clearly shown in the article by Heemskerk et al. in this issue of the *Journal*.[1] This randomized, controlled study of tuberculous meningitis in Vietnamese adults, probably the largest ever undertaken, was carefully planned and executed and evaluated an intensified regimen that included both a higher dose of oral rifampin than the standard dose (15 mg per kilogram of body weight vs. 10 mg per kilogram) and the addition of levofloxacin to the standard regimen that has been used for almost 40 years. It is disappointing that there was no advantage associated with the use of this intensified treatment regimen, with regard to overall mortality (28%) and most measures of illness; indeed, the mortality associated with both the standard regimen and the intensified regimen, when clinical disease staging was taken into account, was no better than that associated with the standard therapy of isoniazid, para-aminosalicylic acid, and streptomycin that was used in treatment from 1952 to 1970.[2] Another recent trial, conducted in Indonesia and involving a much smaller number of patients with tuberculous meningitis, assessed treatment with another fluoroquinolone — moxifloxacin — at a standard dose of 400 mg and at a higher dose of 800 mg, as well as treatment with a higher rifampin dose (13 mg per kilogram) administered intravenously. The 6-month mortality associated with the lower and higher doses of moxifloxacin (42% and 63%, respectively) did not differ significantly from that associated with the regimen without moxifloxacin (45%); however, mortality was lower among patients who received the higher rifampin dose administered intravenously than among those who received the standard oral rifampin dose of 10 mg per kilogram (34% vs. 65%)[3]. Further exploration of higher doses of rifampin may yet lead to improvements in the outcome of tuberculous meningitis.

Coupled with the recent findings of the failure of fluoroquinolone treatment to contribute