

Preface

The field of obesity and the metabolic syndrome continues to advance on all fronts. This book is an effort to bring together a series of chapters that cover many of the newer facets of the problem. We have tried to capture the goal of this book in the subtitle “from bench to bedside”. Fundamentally, as human biologists, we are interested in understanding the problem of obesity and the metabolic syndrome and then applying this new knowledge to easing the burden of people afflicted in this disease state. We begin with the laboratory findings. Butler and his colleagues begin the process with an illuminating discussion of the factors that control the termination of meals. After a brief review of the neuroendocrine control system, they provide a detailed look at the gastrointestinal and pancreatic factors that can stimulate or inhibit food intake. They then look at the long-term control affected by leptin and insulin. In the next chapter, Dr. Chumlea discusses the various methods for measuring “obesity”. Dual-energy absorptiometry (DXA) has the ability to provide estimates of fat mass, lean mass and bone mass making it quite versatile. However, from a practical perspective, weight, waist circumference and the body mass index (body weight in kg divided by the square of height in meters) are the most useful. The body mass index (BMI) has been the most widely used index in the assessment of the current changes in prevalence of obesity, providing a good picture of the increasing epidemic of obesity. The progress of this epidemic has been well characterized by Dr. Mokdad from the Centers for Disease Control and Prevention, the U.S. Governmental agency charged with tracking this epidemic. Genetic factors are clearly behind the susceptibility to obesity that characterizes this epidemic. Dr. Comuzzie, who has contributed important information to this problem, focuses on the advances that we have experienced in understanding the relations of nature and nurture. In a well written and timely chapter, Drs. Levin and Clegg argue the case of a “set-point” or a defended body weight. They begin with the historical and anatomic data and the move to discussing the intricacies of the mechanisms that control this process. Fat is the site for storage of extra energy. When the fat cells reach their maximum storage capacity, new fat cells may be recruited, but fat may also be stored ectopically in other organs. Tchkonina, Corkey, Kirkland explore this important new concept in a chapter dealing with lipotoxicity. The conditions for lipotoxicity occur when net capacity to store and utilize lipids is exceeded in diseases

such as diabetes, obesity, the metabolic syndrome, indexmetabolic syndrome lipodystrophies, aging, and other conditions. The chapter by Toledo and Kelley extends this concept of lipotoxicity to the issues associated with visceral adipose tissue. This ectopic storage of fat is associated with insulin resistance. This group has coined the term “metabolic inflexibility” to describe the setting in which an infusion of insulin fails to enhance carbohydrate metabolism in muscle. They develop the “portal hypothesis” which suggests that visceral adipose tissue provides fatty acids to the liver than lead to accumulation of lipid there and in the intramyocellular compartment. Fatty-acyl-CoAs, diacylglycerol and ceramides are important candidates for these metabolic changes. As demonstrated by several groups, this effect is associated with changes in mitochondrial genes and their enzymes that are involved in oxidative phosphorylation. Finally, they discuss the lipodystrophic states where loss of fat is associated with increased insulin resistance. Recent studies show that replacing leptin, a product of the fat cell, to individuals with too little fat can ameliorate most of the metabolic features of lipodystrophy. Drs. Lemieux and Despres, leaders in the field of studying visceral adipose tissue and the metabolic syndrome provide a succinct summary of the advances in this area. Children who become overweight bear the stigma associated with obesity, and at the same time experience the detrimental health benefits that are often seen. Caprio and Weiss, who have been leaders in establishing criteria for the metabolic syndrome in adolescents, review their data and the types of changes that characterize this condition in the adolescents in their clinic. From the laboratory side of the problem, we now turn to translating these findings into the evaluation and treatment of obesity and the metabolic syndrome. Evaluating any patient is the first step in deciding how serious the problem may be and what steps to take in correcting it. Ryan and Bray provide the introductory steps in this process with a chapter dealing with evaluation of the patient with obesity and the metabolic syndrome. It is now clear that measurement of waist circumference along with the BMI provide the first steps. For establishing the metabolic syndrome other measurements such as blood pressure, a lipid panel and glucose are needed. If two of these are abnormal and there is an enlarged waist one can diagnose the metabolic syndrome. Once the diagnosis is made, treatment is in order. Since all of the components of this syndrome will respond positively to weight loss, strategies to help people lose weight are the first steps. However, when the lipid, blood pressure or glucose abnormalities remain abnormal, they should be treated with one of the appropriate therapies. Lifestyle strategies are the first line of approach. Diet, exercise and behavioral therapy make up the 3 components of these lifestyle approaches. Diet is the first line of attack and the chapter by Foster and Makris introduces us to this problem. Their chapter provides a nice review of the low carbohydrate diets in comparison with other diets. Foster and Makris first review the low and moderate fat diets and the turn

to the low carbohydrate diets and provide us a feeling for the value that each of these groups of diets have in the treatment of overweight. Diets reduce energy intake and thus require overweight individuals to draw fat from their fat stores. Exercise, reviewed by Jakicic and Otto, works by increasing the utilization of energy through physical exertion. They begin by convincing us that those who are more active have improved health benefits and longevity. They then review the literature on weight loss studies and show that exercise alone is not a very effective strategy. However, for maintaining weight loss, becoming and remaining more active clearly plays a central role. The third arm of lifestyle is behavior therapy whose role is reviewed in a chapter by Williamson, Stewart and Martin. They provide an historical background and then describe the many features that come under this category. The use of portion controlled foods and the use of the internet are two of the more recent advances, each of which offers the hope of extending the scope and success of this approach. Obviously we would prefer to prevent overweight than to have to treat it. Kumanyika and Daniels take us through the literature on studies that have attempted to prevent the progression of overweight. Two broad kinds of approaches have been taken—population wide approaches and targeted approaches. In spite of much work, the authors correctly note that at present we have no definitive studies to guide a clear approach to the problem. Where prevention fails, therapy is needed. Two drugs are currently approved by the U.S. Food and Drug Administration for treatment of obesity. Dr. Wyatt discusses the use of these two drugs, sibutramine and orlistat. Although both are effective in producing weight loss, the loss is moderate and often frustrating to the participant who is taking the drug. Although only 2 drugs are currently approved, Greenway and Bray review the burgeoning new drug armentarium. Several drugs approved for use in diabetes, like metformin, pramlintide and exenatide produce weight loss. Rimonabant, an antagonist to the cannabinoid CB1 receptors in the brain is a promising new agent that will soon be evaluated by the FDA for approval and clinical use. There is cautious optimism that it may change the landscape of treatment for those individuals whose overweight has not been prevented. The final chapter deals with surgical interventions for overweight patients. Since laparoscopic techniques for this procedure became wide spread, its performance and safety have both changed significantly. Over 100,000 operations were performed last year, and the number continues to rise. With this final chapter, we complete our tour from laboratory to clinic. We hope it meets the needs for which it was put together—a survey of new strategies to bring the laboratory to the clinic for treatment of obesity and the metabolic syndrome.

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