

Sleepless in America

A Pathway to Obesity and the Metabolic Syndrome?

WHETHER ONE IS READING RECENT REPORTS from the Centers for Disease Control and Prevention, articles in the scientific literature or popular press, or just glancing around and looking at people in the subway or the shopping mall, it is apparent that there is a major epidemic in America: obesity! Obesity is a disease that, in just the past few decades, has been rising dramatically in developed countries and reached epidemic levels in the United States. Data from the Behavioral Risk Factor Surveillance Program (available at: www.cdc.gov/brfss) have revealed a striking increase, over the past 15 years and across the United States, in the prevalence of overweight (body mass index [BMI, calculated as weight in kilograms divided by the square of height in meters], 25-30) and obesity (BMI >30), and there is recent evidence of an alarming rise in the proportion of children affected with the disorder. Besides the social stigma attached to obesity, these trends are cause for concern because of the risks of secondary complications, including insulin resistance and type 2 diabetes mellitus, hyperlipidemia, cardiovascular disease, hypertension, stroke, cancer, and arthritis. The increase in levels of proinflammatory cytokines and prothrombotic factors associated with obesity is now recognized as an independent cause of morbidity and has been targeted by the National Cholesterol Education Program Adult Treatment Panel as an important independent contributor to cardiovascular risk.¹ Many fingers are being pointed at many causes: not enough exercise, high-fat foods, poor eating habits, watching too much television, genetics, family history, fast-food hysteria, or exposure to advertising luring us to eat unhealthy foods. Even our early prenatal and postnatal environments may be putting us on a trajectory for an unhealthy metabolic state later in life.² A common denominator may be the excessive intake of carbohydrates encouraged by the wave of "low fat" dieting that began in the 1970s. We can even blame our genes, which evolved in humans engaged in high physical activity (much of it chasing and looking for food) with eating habits requiring one to eat as much as possible (and as much meat and fat as possible) when a meal became available, ie, rarely, as opposed to having the food lying around us all of the time.

In recent years, a new and unexpected "obesity villain" has emerged, first from laboratory studies and now, as reported by Vorona et al³ in this issue of the ARCHIVES, in population-based studies: insufficient sleep. In a study analyzing 924 patients from 4 primary care practices in Virginia, a reduced amount of sleep

was associated with overweight and obese status, and patients in the obese group showed a near inverse linear relationship between weight and reported sleep time. The relationship between obesity (and associated metabolic and cardiovascular disorders often referred to as the metabolic syndrome, or syndrome X⁴) and insufficient sleep has only emerged in the past 5 years. In a pioneering study in 1999 by Van Cauter and colleagues,⁵ it was found that sleep restricted to only 4 hours per night for 1 week led to endocrine and metabolic changes associated with diabetes (insulin resistance) and weight gain in healthy young men. While the effects were reversible with normal sleep times, these remarkable, and at the time surprising findings, led basic and clinical researchers off on the trail to find the physiological linkages between insufficient sleep and metabolic function. This work also renewed interest in the role of insufficient sleep as a cause of many of the metabolic abnormalities associated with sleep apnea. However, while there is a growing awareness among some sleep, metabolic, cardiovascular, and diabetes researchers that insufficient sleep could be leading to a cascade of disorders, few in the general medical profession or in the lay public have yet made the connection.

See also pages 25, 35, and 42

For most of us, the news about weight control strikes home as pounds accumulate with aging or reappear after dieting. Unfortunately, most of the weight-conscious public, and even the health-care professional community, still view weight control as a biological black box and ascribe obesity to indolence and a lack of will. The experience of those whose body weight is "defended" despite dieting would suggest otherwise—that weight is controlled much like a thermostat, with fluctuation around a programmed set point. Yet the obesity magic bullet has proved elusive because, like other complex diseases (eg, hypertension, hyperlipidemia, and cancer), multiple genetic and environmental factors contribute to body weight dysregulation and its secondary complications. An important goal in developing new therapies for obesity and the metabolic syndrome is to gain a greater understanding of the elaborate pathways that regulate appetite, food intake, and energy expenditure and to unravel interactions between behavior, metabolism, and environment that contribute to long-term energy constancy. It is of particular interest now to determine the mechanisms by which acute and/or chronic sleep loss alters this complex metabolic machinery, as well

as the role of the circadian clock in its regulation of the timing of sleep and metabolic function.⁶

Another article in this issue of the ARCHIVES may be related to the association between sleep loss and obesity found in the article by Vorona et al.³ Ferreira et al⁷ report on data from the Amsterdam Growth and Health Longitudinal Study and they determine that, starting at 13 years of age, factors such as fatness, fitness, and lifestyle are important determinants of the metabolic syndrome that affects 10% of the studied population by the age of 36 years—an indication that the obesity epidemic in young people is not confined to America. An alarming statistic defines a major problem among American youth: between 1980 and 2000, the rate of obese young people has risen from 5% to 15%, and another 15% has moved into that classification in young adulthood. While this epidemic in our young population has received national attention, less well-known is the finding that children of all ages in America are sleeping 1 to 2 hours less per night than they need, according to a recent poll taken by the National Sleep Foundation.⁸ While insufficient sleep has often been associated with the elderly population, the increasing demands and lifestyles of modern society have imposed restricted sleep on our youth as well. It is now critical to determine the importance of a lack of sufficient sleep during the early formative years in putting our youth on a trajectory toward obesity and the metabolic syndrome—a trajectory that could be altered if sleep loss is indeed playing a role in this epidemic.

A new edited book, *Obesity in Childhood and Adolescence*,⁹ will hopefully raise the clinical community's awareness of the causes, consequences, and therapies of obesity in the young. However, it is noteworthy that none of the 21 chapter titles in this book contain the word *sleep*, indicating that the connection between sleep loss and obesity still is not a major consideration in the war on obesity. Hopefully, articles such as those in this issue of the ARCHIVES, which, on the one hand, link sleep loss and obesity, and on the other hand, define the importance of early habits for obesity and the subsequent development of the metabolic syndrome, will lead more clinicians to explore the effects of chronic long-term partial sleep loss on weight and metabolic function in our children.

It is fascinating to note that genetic and clinical observations both point to interconnections between sleep and metabolic regulation. The discovery of the orexins as neuropeptide agonists of orphan signaling pathways within the energy center of the brain,^{10,11} and the subsequent identification of the orexin receptor as the causative genetic defect in the most common form of canine narcolepsy by Mignot and colleagues,¹² set the stage for investigating neural interconnections linking sleep and metabolic homeostasis. While these 2 fundamental systems appear to have distinct functions in human physiology, the discovery of overlapping molecular components suggests a coregulation that may have coordinated the alternance between periods: periods of fasting and

sleep and periods of wakefulness, food seeking, and energy storage. A lack of sleep may perturb the homeostatic coordination of these pathways, activating metabolic pathways that trigger energy conservation (increased food intake and decreased expenditure) in excess of the energy cost of increased wakefulness. Indeed, our recent analysis of leptin-deficient animals suggests that leptin per se may be necessary for consolidated sleep, since animals with a genetic absence of leptin display markedly increased sleep fragmentation and experience increased periods of microsleep during the active period.¹³ In view of observations from experimental models and human clinical studies on the relationship between the sleep-wake cycle and fuel homeostasis, it may be opportune to ask whether intervention in sleep disorders may ameliorate some of the metabolic deficits associated with overweight and obesity.

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