Preface

Narcolepsy is characterized by excessive daytime sleepiness, cataplexy, fragmented sleep, and other symptoms. It affects approximately 1 in 2,000 people and can have a huge impact on their ability to succeed in school and work. Narcolepsy was first recognized by clinicians over 125 years ago, yet until recently, its cause remained a mystery. In 2000, two research groups discovered that narcolepsy is caused by a selective loss of neurons in the hypothalamus that produce the hypocretin neuropeptides (also known as orexins). With this groundbreaking perspective, narcolepsy research has advanced in large steps, with new discoveries every year that have enhanced our understanding of the disorder.

In 1975, the First International Symposium on Narcolepsy was held in La Grande Motte in France, organized by William C. Dement, Christian Guilleminault, and Pierre Passouant. After a successful Fifth International Symposium on Monte Verità near Ascona (Switzerland) in 2004, many of the world's leading narcolepsy researchers – including the authors of this book – gathered again in this inspiring landscape for the Sixth International Symposium on Narcolepsy in 2009. In the course of the meeting, it became clear that researchers and clinicians have learned much about narcolepsy, yet many key questions remain unanswered, even in light of recent advances.

For instance, we still have no definite proof that narcolepsy is caused by an autoimmune attack or by another mechanism. The recent discovery that levels of specific antibodies are increased in some patients soon after the onset of narcolepsy provides some of the most compelling evidence for an autoimmune mechanism, but many questions remain unanswered. For example, it appears that narcolepsy is caused by a selective loss of the hypocretin-producing neurons, yet the target antigens are expressed by many non-hypocretin neurons. In addition, antibody titers appear normal in many narcolepsy patients. It remains possible that these antibodies are not pathogenic but are simply increased as a consequence of another process that kills the hypocretin neurons. Much more work is needed to determine what mechanism kills the hypocretin neurons in narcolepsy.

Many questions remain about the pathophysiology of cataplexy, hypnagogic hallucinations, and sleep paralysis. These symptoms have many similarities to rapid eye movement (REM) sleep, such as muscle atonia and dreaming, and they may represent the intrusion of fragments of REM sleep into wakefulness. Theories have proposed an increase in REM sleep pressure, a reduction in the threshold to transition into REM sleep, or dysregulation of

the brainstem mechanisms that normally coordinate REM sleep phenomena. However, there is little evidence that these symptoms are influenced by manipulations of REM sleep, and gamma hydroxybutyrate strongly suppresses cataplexy yet it has no effect on REM sleep. Thus, the pathways underlying cataplexy and other narcolepsy symptoms remain elusive.

Furthermore, people and animals with narcolepsy transition frequently and rapidly between wakefulness and sleep. For over 20 years, this pattern has been referred to as behavioral state instability but its cause remains unknown. It is possible that hypocretin/orexin stabilizes the neural pathways that regulate sleep/wake transitions; so a loss of the hypocretin neurons would destabilize this mechanism, leading to frequent transitions between wakefulness and sleep. This could account for both excessive daytime sleepiness and fragmented nocturnal sleep in narcolepsy. However, this hypothesis is not yet proven, and the electrophysiological basis of this instability is still poorly understood.

Last but not least, narcolepsy is often accompanied by a variety of metabolic and psychiatric symptoms, including obesity and depression. These symptoms are unappreciated by many clinicians and their fundamental cause remains unknown. For instance, there is still no clear explanation why narcolepsy patients are often overweight. Hypocretin can enhance appetite, yet individuals with narcolepsy probably eat normal amounts. Their obesity may result from low physical activity or low basal metabolic rate.

Thus, despite much recent progress, many large questions remain about the causes, neurobiology, and physiology of narcolepsy. To provide a unified resource for clinicians and basic scientists, dozens of researchers with expertise in nearly all facets of narcolepsy have contributed to this book. Our intent is to provide a comprehensive and up-to-date overview on the pathophysiology and neurobiology of narcolepsy and to describe new clinical research on narcolepsy and the best approaches for treatment. The supplementary DVD offers a unique and large collection of movies displaying the symptoms of narcolepsy in people and animals. We have also highlighted many of the outstanding questions about narcolepsy, and hope this book will spark new perspectives and inspire new discoveries.

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