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## Introduction to Special Issue in Sleep Medicine: Advances in Sleep Medicine

Robert McCarley, MD\* and Sudhansu Chokroverty, MD

### Abstract

The field of sleep medicine is in a welcome stage of rapid advance, but at a pace that leads to a sometimes overwhelming overload of knowledge for both clinicians and researchers. The nine papers in this issue are designed to give the reader an organized overview of current thinking and background in Basic Science, Clinical Science and Therapeutic Measures, the major divisions of this special issue.

An important trend is the increasing development of basic science knowledge relevant to understanding and treating the clinical features of sleep disorders.

The therapeutic advances section covers both the treatment of narcolepsy and the role of non-invasive ventilation. The recent neurobiologic knowledge that narcolepsy-cataplexy results from a deficiency of the hypothalamic neuropeptide hypocretin (orexin) has opened the exciting possibility of using novel therapies. Despite this new knowledge, traditional stimulants and antiepileptic agents including modafinil, a novel wake-promoting agent and selective serotonergic, adrenergic and dopaminergic reuptake inhibitors and recently introduced sodium oxybate remain the mainstay of treatment for this condition.

To whet the reader's appetite and to offer a road map for possible reading, we briefly summarize the content of the papers.

### Basic Science

- Szymusiak and collaborators provide the reader with information on hypothalamic control of sleep, describing the ventrolateral preoptic area (vlPOA and extended vlPO) and the median preoptic nucleus (MnPN) and their role in NREM and REM sleep. The authors describe their own important work in extracellular recordings and cFos studies in these regions. The evidence is consistent with a key role of promoting sleep onset and sleep maintenance, with evidence for "sleep-active" neurons in these regions as well as basal forebrain.
- McCarley provides an extensive survey of mechanisms of REM and NREM sleep. The survey of neuronal and neurotransmitter-related brainstem mechanisms of REM includes monoamines, acetylcholine, the reticular formation, a new emphasis on GABAergic mechanism and a discussion of the role of orexins in diurnal control of REM sleep. The focus of the NREM sleep discussion is on the basal forebrain and adenosine as a mediator of homeostatic control and perhaps mediating some of the cognitive consequences of sleep apnea.

\*Corresponding Author: Professor and Head, Harvard Department of Psychiatry, VA Boston Healthcare System, 940 Belmont St., 02301, Brockton, MA, United States, Phone: 508-583-4500, x63723 Email: robert\_mccarley@hms.harvard.edu

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- Stickgold and Walker describe the exciting new findings related to memory consolidation during sleep. Evidence strongly suggests procedural motor and sensory memory is importantly dependent on sleep, while sleep is less clearly related to declarative memory. A related topic, that of brain plasticity during sleep, which may form the basis of memory consolidation, is surveyed from the viewpoints of imaging, EEG and molecular/cellular studies.
- Ondo and collaborators describe animal models of the clinical features of restless legs syndrome (RLS) using lesions of the hypothalamic A11 dopaminergic cells (which project to the spinal cord), dopamine D3 receptor knockouts and reduction of iron intake. Development of an animal model of periodic leg movement syndrome has begun.

## Clinical Science

- Dang-Vu and colleagues survey the rapidly developing field of neuroimaging in sleep medicine. In normal NREM sleep there is a global decrease in cerebral blood, especially in the brainstem, thalamus and basal forebrain. In contrast, REM sleep is characterized by metabolic and hemodynamic evidence of activation of the pons, thalamus and basal forebrain. Of particular interest is the deactivation of the dorsolateral prefrontal cortex, perhaps related to absence of executive control and unification during dreams, and also the amygdala activation, perhaps related to emotions during dreams. Sleep in insomnia patients is associated with enhanced brain metabolism, which is in line with the concept of a “hyperarousal” state. Beginning neuroimaging work in patients with obstructive sleep apnea, narcolepsy, restless legs syndrome, fatal familial insomnia, parasomnias, and depression is described.
- Nishino describes both the clinical and pathophysiological features of narcolepsy. Narcolepsy is remarkable for the knowledge of how loss of the hypocretin/orexin peptide neurotransmitter is associated with the clinical features of the disorder. It is the most perfectly understood disorder of sleep and, indeed, one of the best understood of all human diseases. The discovery of the basis of canine narcolepsy (receptor abnormality) and rodent knockouts of the receptors and precursor peptide paved the way for understanding human narcolepsy. The current treatments for narcolepsy of modafinil and gamma hydroxybutyrate, as well as amphetamines and antidepressants are discussed.
- Banno and Kryger describe the clinical features of obstructive sleep apnea syndrome (OSAS), including snoring, repetitive apneic episodes, and daytime sleepiness; its origin in upper airway obstruction; its consequences of daytime sleepiness, neurocognitive dysfunction, development of cardiovascular disorders, metabolic dysfunction, and impaired quality of life; and its treatment with continuous positive airway pressure (CPAP), oral appliances, and surgery. OSAS is contrasted with the central sleep apnea syndrome (CSAS), characterized by cessation of breathing which stems from a reduced CNS respiratory drive. CSAS is common in patients with heart failure and cerebral neurologic diseases, has sleep apneic episodes without polysomnographic evidence of airway obstruction, and is treated with oxygen, adaptive servo-ventilation, or CPAP.

## Therapy

- Thorpy gives a comprehensive review of the advances in the treatment of excessive daytime sleepiness and cataplexy, the two most disabling symptoms of narcolepsy syndrome. He provides an in-depth description of the two leading drugs, modafinil and sodium oxybate, found to be useful in narcolepsy-cataplexy. In light of the recent

understanding of the pathophysiology of narcolepsy-cataplexy, Thorpy alludes to emerging new therapies (e.g., hypocretin cell transplantation and immunomodulation) that may be available in the future, after further basic and clinical investigations.

- In the final chapter, Robert provides a comprehensive account of the role of noninvasive ventilation for treating respiratory failure in neuromuscular and other sleep-related breathing disorders. The contemporary treatment for hypoventilation noted in neuromuscular and other disorders is non-invasive intermittent positive pressure ventilation (NIPPV), which has virtually replaced tracheostomy, an invasive procedure with all the undesirable side effects as well as cumbersome negative pressure ventilators. The NIPPV has shown significant improvement in quality of life and possibly also survival of many of these patients with inexorably progressive neuromuscular disorders.