Multi-author Review
Sleep and sleep disturbance

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Sleep and sleep disturbance: from genes to dreams

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Sleep remains one of the great mysteries of biomedical science. Few physiologic processes are as fundamental to health and function, so universal in daily experience, and so poorly understood. Sleep is important beyond keeping us awake, although we all greatly appreciate that aspect of it. Sleep disturbance is associated with doubling of mortality rate in older adults [1] and is associated with increased risk of depression [2], diabetes [3], dementia [4], high blood pressure [5] and many other chronic diseases [6]. Chronic insomnia erodes quality of life and imposes enormous costs in both lost productivity and increased health care utilization [7, 8]. There is clearly more to 'a good night's sleep' than simply slumber.

Sleep begins at the cellular and molecular levels, but it is also sensitive to whole-organism and environmental influences. For example, humans can override (at least temporarily) the biological sleep drive in order to respond to crises, work requirements or social pressures. Humans also experience unwanted disruptions in their sleep that are due to disturbed genetics, internal biological circuitry, or external factors such as noise and stress. This multi-author review discusses these dimensions of sleep and sleep disturbance, contextualized within the continuum of research into these topics moving from 'bench' to 'bedside'; that is, from cellular to community.

The topic of sleep and sleep disturbance is ideal for a multidisciplinary journal like Cellular and Molecular Life Sciences (CMLS). As can be seen from the collection of articles we have pulled together, interdisciplinary and multidisciplinary perspectives on sleep science cover a lot of ground. We believe that exposure to this diversity can contribute to broader, more coherent understanding. We organized the information to flow from bench to bedside in order to give the readership of CMLS the opportunity to locate their own interests from biological to biomedical contexts along this continuum, or to observe that/how their own work is relevant at many different points in the continuum.

The articles we've included are arranged from basic science (i.e. 'bench': biology, anatomy, chemistry) to clinical medicine (i.e. 'bedside': methodology of research and clinical intervention studies in sleep disturbance). This organization reflects our intention to raise awareness of the 'upstream' and 'downstream' effects of research that is ongoing at many levels in the area of sleep. Four articles in section 1 are organized around providing biological background for understanding sleep and sleep disturbance. Three articles in section 2 are focused on methodology in the study of sleep and sleep disturbance.

We acknowledge and indeed emphasize that this is not an exhaustive review of sleep science. We do not cover the parasomnias, narcolepsy, sleep-related breathing disorders and other clinical syndromes. By focusing primarily on sleep physiology and insomnia, we have been able to cover these topics in detail in relatively brief format. We have collected seven articles contributed by international scholars to demonstrate the

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level of sophistication in the literature to date, and to encourage new interdisciplinary work in the area. Again, our intention was not to exhaustively summarize the work going on at all levels (from bench to bedside) throughout sleep science but rather to highlight the continuum itself, and to promote the awareness, and integration, of both the basic and clinical science perspectives in sleep research done at any level.

Nava Zisapel of Tel Aviv University (Israel) begins this issue with an overview of the biological basis of sleep and detrimental effects of sleep disturbance. This article provides a brief overview of sleep physiology, covering important topics such as non-REM and REM cycles, chronobiology, contributions to sleep and sleep disturbance from physiologic mechanisms such as breathing and temperature and discussing the role of sleep in growth and development as well as the impact of aging and neurodegeneration. Discussion of immunology and sleep and the phenomenon of daytime sleepiness provide many concrete links between human and animal physiology and sleep and sleep disturbance in terms of what is known and what remains to be discovered.

The second article in the biological section of this issue leads directly from many of the ideas summarized by Zisapel. In our second article, Dag Sternberg of the University of Helsinki (Finland) reviews cutting edge research into the neuroanatomy and neurochemistry of sleep. This article includes discussion of specific central nervous system (CNS) nuclei and structures involved in sleep and alertness, as well as focus on the neurochemistry of sleep and wake.

The chronobiology of sleep in humans is reviewed in depth in the third article by Leon Lack and Helen Wright of the Flinders University of South Australia. Their article focuses on the neurophysiology of circadian rhythmicity, including coverage of the biological clock, its anatomy and function, disorders of the circadian system and the primary zeitgebers: ambient light and the pineal hormone, melatonin.

The final article in the biology section of this issue is truly a bridge topic, focusing on the genetics of sleep and sleep disorders. In this article, Mayumi Kimura and Juliane Winkelmann of the Max Planck Institute for Psychiatry (Germany) discuss genetic influences on sleep and sleep disorders as well as the phenotypes that are critical for the optimization of research methodology. Kimura and Winkelmann discuss disorders of sleep and arousal, and their review focuses on genetic vs. non-genetic causal mechanisms. This article is one of the few in our issue that specifically focuses on clinically defined sleep disorders, and they review their classification and diagnosis, and give prevalence figures across the lifespan. Specific genotypes and phenotypes may have implications for pharmacological as well as genetic interventions, and these are discussed as well in this article.

The article by Kimura and Winkelmann provides a natural segue from the first section, focusing on the biological underpinnings of sleep and sleep disturbance, to the second section, which focuses on issues closer to the 'bedside' end of the bench-to-bedside continuum, emphasizing methodology in the study of sleep and sleep disturbance. Our first article in this section is crucial to the development of future research in sleep and sleep disturbance; Tom de Boer of Leiden University (The Netherlands) discusses the technology of sleep research. His review includes comparisons of techniques used in humans and nonhumans, including animal models of sleep disturbance. Because of the role of development and aging in our understanding of sleep as well as the prevalence of sleep disturbances, de Boer's article also discusses variation in technologies that are used across organism development (fetal to aged). Finally, this article discusses chemical, electrical and physical measurements, surveys, and correlations between these – that is, how sleep researchers use/need tools ranging from genetics to sleep symptom surveys to understand, study and treat sleep disturbances.

The second article in the methodology section, by Mitsuyuki Nakao, Akihiro Karashima and Norihiro Katayama of Tohoku University (Japan), is devoted to mathematical and statistical models of sleep and rhythms. These are crucial tools in the integration of basic science knowledge about sleep and sleep disturbance, and provide structure for the interpretations, objective and subjective, of the variety of inputs and outcomes for sleep and sleep disturbance at each point in their investigation. Of particular interest in research closer to the bed than the bench are statistical concerns in the study of sleep and sleep disorders and the two-process model. Nakano and colleagues describe the role and importance of mathematical modeling, discussing at what point a mathematical model makes sense, and how they can be integrated into a broader sleep medicine research program. Importantly, the Nakano et al. article discusses critical assumptions in deploying mathematical and statistical models in the study of sleep and sleep disturbance; these considerations are relevant for any stage of research.

The final article in the issue discusses some methodologies and considerations in clinical sleep research. Agostinho Rosa, from the Instituto Superior Tecnico (Portugal) and colleagues Dalva Poyares, Walter Moraes and Fatima Cintra from the Universidade Federal de Sao Paulo (Brazil) orient the CMLS

audience to issues and considerations at the bedside portion of the bench-to-bedside continuum, a reminder that the entire continuum is informative for the study of sleep and sleep disturbance within the clinical context. Rosa and colleagues describe the ways in which REM and nonREM sleep are targeted for interventions and can be utilized as outcomes. Dream research can have a significant role in the continuum from bench to bedside in sleep and sleep disturbance research, and their article addresses this topic as well. This multi-author review was designed to summarize and provide extensive references for researchers interested in further information regarding physiology, neurochemistry, chronobiology, genetics, technology, mathematical modeling and, finally, clinical considerations relevant to sleep and sleep disturbance. We think we have assembled an intriguing and unique assortment of topical review articles. We hope you enjoy them and return to them repeatedly for learning, pleasure and inspiration.

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1 Dew, M. A., Hoch, C. C., Buysee, D. J., Monk, T. H., Begley, A. E., Houck, P. R., Hall, M., Kupfer, D. K., and Reynolds, C. F. (2003) Healthy older adults' sleep predicts all-cause mortality at 4 to 19 years of follow-up. Psychosom. Med. 65, 63 – 73.
2 Perlis, M. L., Smith, L. J., Lynes, J. M., Matteson, S. R., Pigeon, W. R., Jungquist, C. R. and Tu, X. (2006) Insomnia (2006) as a risk factor for onet of depression in the elderly. Behav. Sleep Med. 4, 2, 104 – 113.
3 Yaggi, H. K., Araujo, A. B. and McKinlay, J. B. (2006) Sleep duration as a risk factor for the development of Type 2 diabetes. Diabetes Care. 29, 657 – 661.
4 Cricco, M., Simonsick, E. M. and Foley, D. J. (2001) The impact of insomnia on cognitive functioning in older adults. JAGS 49, 1185 – 1189.
5 Gottlieb, D. J., Redline, S., Nieto, F. J., Baldwin, C. M., Newman, A. B., Resnick, H. E. and Punjabi, N. M. (2006) Association of usual sleep duration with hypertension: the Sleep Heart Study. Sleep 29, 1009 – 1014.
6 Doghramji, K. (2006) The epidemiology and diagnosis of insomnia. Am. J. Managed Care 12, S214 – S220.
7 Silber, M. H. (2005) Chronic insomnia. NEJM 353, 803 – 810.
8 Summers, M. O., Crisostomo, M. I. and Stepanski, E. J. (2006) Recent developments in the classification, evaluation, and treatment of insomnia. Chest 130, 276 – 286.