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Great challenges to sleep medicine: problems and paradigms

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> "There are known knowns. These are things we know that we know. There are known unknowns. That is to say, there are things that we now know we don't know. But there are also unknown unknowns. These are things we do not know we don't know."
>
> -United States Secretary of Defense Donald Rumsfeld, 2002

Echoing a key observation from Karl Raimund Popper, that "*there are known knowns…*[1]" former US Defense Secretary Donald Rumsfeld commented in 2002 on the increasingly unstable situation in post-invasion Afghanistan. Mr. Rumsfeld's statement was widely viewed as elusive but nevertheless possessed a profound and almost philosophical truth. The generalization that what we do not know is considerably greater than what we do know is certainly true in the field of sleep medicine. This truth has become increasingly apparent despite the many research accomplishments that have already been made in the last few decades. As we reflect on these accomplishments it is also clear that much remains to be done.

Over the last decade there has been an unprecedented growth in our basic understanding of the brain processes which occur across behavioral states. Compared to previous decades, we now know more about the neurotransmitters and neuromodulators that promote and regulate sleep/wakefulness and which brain structures and neuronal ensembles are involved. Despite these advances in our understanding, there are still basic questions about sleep that remain unanswered.

As we now know, sleep is a complex behavior which continues to be an evolutionary puzzle. Every animal adequately studied to date engages in some form of sleep or sleep-like behavior (Lima et al., 2005; Siegel, 2005, 2008; Cirelli and Tononi, 2008) Moreover, sleep is an essential part of our daily rhythm (Deboer et al., 2003), although the purpose it serves is one of the unresolved problems in modern biology. Although one may ascribe any number of physiological functions to sleep, the issue of exactly what function it serves, at least at its most fundamental level, remains unknown.

Despite rigorous research efforts, the question still remains: can we, in the foreseeable future, determine why organisms sleep? What evolutionary function is served by this activity? That being said, what holds the key to answering these questions?

Despite a number of comparative phylogenetic studies that have been carried out to date, there are many additional unknowns and questions about sleep arise that still remain to be addressed (reviewed elsewhere, Allada and Siegel, 2008). First, the current definition for sleep doesn't apply to all living organisms, and therefore does not account for all of its characteristics. Second, throughout the animal kingdom, sleep activity varies considerably not only in its architecture, but also in terms of its behavioral and physiological expression. These differences occur among closely related genera and species as well as between mammals and non-mammalian species. Third, there are variations in sleep duration in animals that are studied in captivity vs. those that are studied in their natural habitats. Fourth, sleep in terrestrial mammals and avian species does not exhibit a unidimensional brain state. Finally, many of the current hypotheses concerning sleep suffer from being divergent and/or speculative, or conversely, too limited in scope, problems which are not unexpected given the insufficient research evidence which exists in many areas.

Before we can have an adequate definition of sleep therefore, we will need to address the significant gaps which exist in our knowledge. In particular, the current definition of sleep should be modified to include species variations. The lack of comparative phylogenetic analysis will need to be dealt with before an adequate understanding of the mechanisms and functions of sleep can be developed.

Over the years, many hypotheses concerning the functions of sleep have been put forth (Rechtschaffen, 1998) and the list is still growing. However, these hypotheses often overlap and in many cases are simply reflective of differences in the way that researchers and clinicians view a particular problem. In many cases, it does however, suggest that the direct evidence is still lacking. The difference of opinions expressed among researchers further reflects the richness and multiplicity of perspectives within the field. These differences of course, continuously refined our thinking about sleep. Nevertheless, there are often inconsistencies in terms of how scientists might view a particular problem. For example, one of the hypotheses about the functions of sleep is that it helps to consolidate memory. This view is not universally shared however, and others feel that the evidences shed no obvious light and have advocated that sleep plays no role whatsoever in supporting memory functions (Vertes, 2004). The lack of consensus about such fundamental issues indicates that we have only just begun to unravel the mystery of sleep. Part of the reason for disagreements about some of the most basic bedrock issues in sleep research may be the preference for studying the process in humans and other mammals.

However, simpler organisms provide excellent genetic models for studying circadian or sleep-like states and their regulatory mechanisms. For example, genetic clues to the reasons that animal sleep have been found in *Drosophila melanogaster* (fruit fly), *Caenorhabditis elegans* (roundworm), and *Danio rerio* (Zebrafish). Findings from the associated studies have deepened our understanding of clock functioning in sleep and circadian rhythm sleep disorders.

[1]The original quote goes back to Confucius – http://en.wikipedia.org/wiki/Unknown_unknown

The importance of the genetic determinants of biological processes is further demonstrated when a species attempts to adapt to unusual environmental challenges. Like the process of evolution itself, sleep behavior has undergone changes in various species as a response to environmental challenges, the details of which have not always obvious to analytical study. In addition to basic biological requirements, social and geophysical factors have exerted additional adaptive selection pressure in determining the way an organism sleeps. It is possible that many of the apparent inconsistencies in theories about sleep function have arisen because they have not adequately accounted for how this behavior is modified by the adaptive demands which vary among species.

Efforts to address many of the larger questions about the nature and function of sleep will undoubtedly have to be postponed until progress is made in understanding key issues in biology. Just as there are controversies surrounding how and when various species evolved on the planet, and in what geophysical environment, the question of when sleep appeared in the evolutionary timescale will probably never be answered. It is nevertheless evident that sleep, at least in the form of quiescence, has ancient origins (Seymour et al., 2004; Kavanau, 2006). However, to address the question of why we sleep it is also necessary to understand the functioning of the brain itself.

The term "restorative sleep" is used frequently in sleep medicine, and is tolerated as a descriptor because it is understood behaviorally and on a common sense level. Nevertheless, in terms of brain energetics, the precise meaning of what has been restored is not clear. To get closer to an answer we will of necessity have to get a better understanding of the life process itself. Despite all the efforts that have been made to do this in terms of cell biology and neurochemistry, it may be necessary to penetrate "behind" these disciplines, and into the realm of physics. The speculation that we need to resort to considerations of energetic fields in order to understand sleep is not universally shared. Most scientists continue to have confidence however that the mysteries of sleep can be unraveled using the tools of biological research.

The field of clinical sleep medicine was spearheaded by pioneers such as Berger (1929) and Aserinsky and Kleitman (1953). In the formative years of sleep medicine, the principal concern of these early investigators (among many others) was to define sleep and to understand its structure and functions in humans. Increasingly however, it has become apparent that the importance of different sleep stages is not unitary phenomenon but varies across species in the animal kingdom. That being said, within the mammalian species, sleep itself is remarkably variable both in terms of quality and quantity.

The bi-directional relationship between sleep quality and the environment has also become a growing area of research interest. Environmental influences also affect sleep. The rapid growth of industrialization, computerization and other technological innovations has brought with it our modern "24-hour society". Although advantageous in many respects, our contemporary way of living has had severe consequences for sleep/wake habits, and this in turn has affected human health and well being. Increasingly our society has become chronically sleep-deprived, and accompanying this phenomenon has been an increase in other health problems. These have included neurological and psychiatric disorders, which in turn produce significant impairments to sleep quality itself. It is estimated that 50 to 70 million Americans suffer from chronic sleep disorders that interfere with their daily functioning (Colten and Altevogt, 2006; the Institute of Medicine report). The negative impact of sleep disorders on productivity, social and recreational activities, and public safety are substantial (Pandi-Perumal et al., 2006; Verster et al., 2008, 2009). Furthermore, these effects can be influenced by racial and ethno-cultural, socioeconomic factors and gender differences. Sleep disorders tend to occur with greater frequency and severity among ethnic and immigrant populations as well as among the socio-economically disadvantaged. There continue to be gaps in our knowledge with respect to the incidence and prevalence of sleep disorders in the populations of most countries.

By far, various therapies that are used to treat sleep disorders are also attracting research interest. Stressful living conditions not only reduce the quality of waking life but also produce sleep difficulties. The growing awareness that difficulties with sleep are not simply a result of stressful living conditions but also reduce the quality of waking life is shown by the rise in the consumption of both hypnotics and alertness promoting medications. Increasingly sophisticated therapies for sleep disorders are also emerging. These, include new pharmacological and non-pharmacological interventions, as well as chronotherapeutic strategies for improving sleep quality. The ethical and legal ramifications of sleep/wake cycle manipulations are issues that remain to be addressed (Ravelingien and Sandberg, 2008).

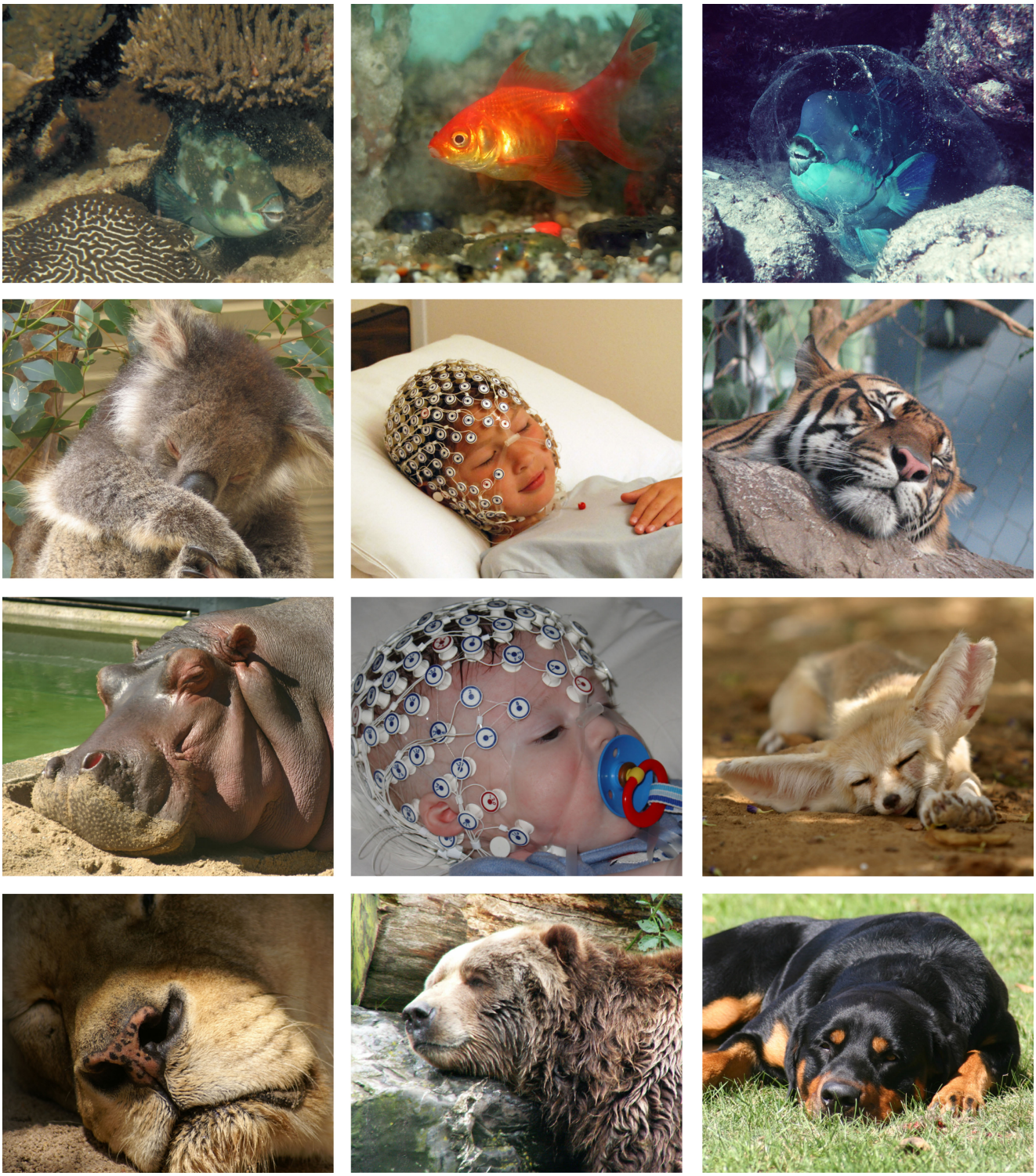
It seems reasonable, nevertheless, to argue that, despite this growth in our understanding of the effects of sleep deprivation on overall health there is still much that we do not know about the interaction between sleep and the environment. For example, inter-individual variation in human chronotypes and circadian rhythms, sleep habits, work schedules, social and environmental stimuli and the effects of sleep on behavior, are still poorly understood (Siegel, 2001; Horne, 2010).

Increasingly, some progress has been made in our understanding of how environmental light/dark (LD) cycles, affect rhythmic processes in humans (e.g. diurnal variation of mood) and the implications of these influences for sleep and wakefulness.

For instance, environmental light, which influences the synchronizing effects of melatonin, is a pervasive *zeitgeber* (time cue or time giver) for the entrainment of circadian rhythms (Vimal et al., 2009). Synchronization of the sleep/wake rhythm and rest/activity cycles with the LD cycle of the external environment is essential for maintaining optimal health and performance (Foster and Roenneberg, 2008); conversely, desynchronization disrupts these cycles and leads to sleep disturbance (Pandi-Perumal et al., 2008).

Another growing area of research interest concerns the effect of sleep on mental health. Sleep disturbance, along with abnormal circadian rhythm regulation, is prevalent in many forms of mental illness (Richter, 1965; Montplaisir and Godbout, 1990; Wirz-Justice, 2006; Pandi-Perumal and Kramer, 2010). Several lines of evidence support the view that the definition of depressive illness should be expanded to include the important role of circadian dysregulation in its development and expression (Pandi-Perumal et al., 2009). In partial support of this view

is evidence that environmental manipulations are effective in treating various sleep disorders, and these are also attracting research interest. In seasonal affective disorder, a major variant of depressive illness, the most effective treatment today is the use of light therapy. When given in a timed fashion, light exposure not only synchronizes body rhythms, it also helps to stabilize mood.



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Although sensitivity to the pattern of melatonin secretion has been long recognized as a behavioral regulator in seasonal animals, its role in mood stabilization has only recently been appreciated. This phenomenon and its therapeutic potential deserve detailed study (Brown et al., 2009a).

Aging is also a factor. Sleep and chronobiological functioning undergo numerous changes with advancing age. These include loss of entrainment stability and responsiveness to *zeitgebers*, changes in clock period and stability, and alterations in clock-regulated processes (Pandi-Perumal et al., 2010), the most salient of which are reductions in the amplitude of melatonin secretion (Cardinali and Karasek, 2010). These changes, which are often accompanied by a desynchronization of the body's intrinsic rhythms, can produce considerable morbidity and distress among the aged.

Melatonin has been found to be useful in treating the disturbed sleep/wake rhythms of circadian rhythm sleep disorders (Brown et al., 2009b). Further research is needed to clarify whether disruption of melatonin secretion patterns is a contributing factor or a consequence of these disorders. Although many theories relating to melatonin and aging have been put forward, the role of melatonin in the aging process is still unknown (Cardinali and Karasek, 2010).

The results of chronotherapeutic strategies are promising and will undoubtedly garner much interest in the coming years (Wirz-Justice, 1987, 2009). Well-conducted, large-scale clinical trials are warranted to further assess the efficacy and safety of chronobiotics/chronotherapy in the treatment of certain sleep disorders.

Sleep Medicine is relatively new field. The influence of sleep disorders on overall health continues to be under appreciated and underreported in the medical literature. As a consequence, patients' complaints about sleeping problems are often not effectively treated. A number of factors contribute to this lack of awareness both at the public and institutional level. One important reason for this is the lack of professional and general education about the impact of sleep on overall health. Other contributing factors include the lack of or limited access to health insurance and therapy, as well as concerns by patients about medication habituation or the inconvenience of some treatment modalities. Additionally, economic issues such as poverty, as well as the escalating cost of treating sleep disorders act as a barrier to treatment and play a major role in the prevalence of sleep disorders in society.

As noted above, there is a need for health awareness programs to educate the general population about the potential consequences of sleep disorders such as sleep loss and chronic sleep deprivation, insomnia, excessive daytime sleepiness, sleep apnea, narcolepsy, shift-work and other circadian rhythm sleep disorders. Such information needs to be made available to policy makers in the public and industrial sectors. Information about the impact of sleep disorders on public health should become a regular part of clinical training initiatives.

Due to the complexity of sleep disorders and their effects, therapeutic management should emphasize a cross disciplinary approach. Sleep centers play a crucial role in the assessment, diagnosis, treatment, and management of sleep disorders, but there are many places and countries where they are not easily accessible or do not exist. Healthcare agencies need to recognize the importance of sleep/wake issues and to provide an appropriate amount of budgeting resources so that these initiatives are prioritized.

The brain, as we now know, is most certainly an organ of enormous complexity and although, the progress in our understanding of the physiology and pathophysiology of the brain in sleep and wakefulness has advanced considerably in recent years, the answers to the fundamental questions are still unknown.

What should we do now? Are we asking the right questions? Should we approach the current theoretical and methodological problems in a more traditional way or should we look for a sort of a paradigm shift? We suggest that by increasing the number of ways that we look at sleep problems, we will be closer to developing an understanding of the core issues involved.

It seems highly likely that the key advances in molecular biology, neurochemistry and neuroimaging will continue to help decipher not only the process, regulatory networks, and critical function of sleep, but will also lead to the development of new therapeutic modalities. As with any scientific and medical discipline, a wider and multidisciplinary team approach to sleep research will help to advance the field.

Simply put, the ultimate challenge for sleep medicine in the coming years will be to bridge the gap between basic and applied clinical research. This can be accomplished by various means:

(a) It appears that the development of translational and applied research will permit the identification of sleep and chronobiological disorders and point the way for effective treatment and management.
(b) Similarly, the development of biomarkers for the diagnosis of sleep disorders and personalized medicine as a strategy for the treatment of sleep disorders will continue to evolve in the future.
(c) It is tempting to speculate that the fields of systemic biology, molecular phylogenetics, neurotechnology, computational neuroscience, and genomics will play an increasingly important role in research in the coming years.
(d) Above all, continued and committed funding of sleep training programs and initiatives such as multisite training programs are essential for promoting sleep research. Such programs offer trainees the tools necessary for the development of collaborative opportunities with peers and other investigators. The Lake Arrowhead sleep training program is an excellent example of such a program whose goal is to engage sleep trainees and sleep specialists in creative thought processes and problem solving, which are essential underpinnings for spurring continued insights into key research areas.

In summary, we have touched upon a few key issues where controversies or unknowns continue to exist in sleep medicine. As we move forward our accumulating knowledge will undoubtedly resolve some of the issues, but additionally will raise new questions, and will most certainly require that we revise our current theories and existing research framework.

Nevertheless, in the immediate context, Popper's observation concerning the vastness of what we do not know still seems particularly relevant to the field of sleep medicine.

> "The more we learn about the world, and the deeper our learning, the more conscious, clear, and well-defined will be our knowledge of what we do not know, our knowledge of our ignorance. The main source of our ignorance lies in the fact that our knowledge can only be finite, while our ignorance must necessarily be infinite."

Popper (1963), From: "Conjectures and Refutations: The Growth of Scientific Knowledge."

Going back to our original question concerning why organisms sleep, do we already know the answer, but because we don't know that we know it, will we, as a consequence, always regard it as too complicated to be deciphered? Well, that is, however, another question.

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