Current status of Sleep Medicine

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Is in not even 50 years back when REM sleep was 1st described by Aserinsky and Kleitman in 1953. In the 49 years since then, however, the field has made tremendous strides and further research is going on to better understand the structure, function and control mechanisms of normal sleep and disorders of sleep.

This review is but only an introductory summary and draws from multiple resources to make you-the members of World Federation of Neurology- aware of some of this exciting work. It is not all-inclusive or complete and is best meant only to ignite the Neurologists and neuro-scientists to be conscious about the clinical and research aspects of sleep medicine and participate in and lead such efforts in their own settings.
Only for sake of convenience have we decided to present this data under 3 categories-

1.Sleep structure and mechanisms
2.Sleep disorders
3.Sleep and public health

Sleep structure and mechanisms:
It has been known that Suprachiasmatic nucleus (SCN) serves as the circadian pacemaker. We are now seeing that non-SCN regions of the brain and many other organs may also express circadian rhythmicity. Circadian photoreceptors may be anatomically and functionally different from visual system. Even within SCN, all the neurons may not have the same phase relationship to one another. Clock genes have been identified. Changes in clock gene(mutations and polymorphism) may affect sleep duration and response to sleep loss. These may also influence the morningness and eveningness in individuals. Alteration in hPer2 gene are associated with Advanced sleep phase syndrome.

A key development is the identification of a new neurotransmitter system in lateral hypothalamus- called Hypocretin(or Orexin) system which plays a key role in control of REM sleep. Defects in this system have clinical implications for disorders of Hypersomnolence e.g Narcolepsy. A canine narcolepsy model has been developed be mutation in Hypocretin receptor 2 gene. Orexin-induced arousal in rats may be mediated by activation of histaminergic neurons in tuberomammilary nucleus. Knocking out preprohypocretin gene results in knock out mice model of Narcolepsy. Post-natal loss of orexin containing neurons in mice also results in Narcolepsy like features in these animals. Direct implications for human narcolepsy are present in the form of hypocretin deficiency as documented by cerebrospinal fluid studies for hypocretin levels.
Newer neuroimaging techniques have shown deactivation of brain in Non-REM sleep and selective activation of specific brain regions in REM sleep. These include- thalamus, occipital cortex, mesiobasal prefrontal cortex and parts of limbic system e.g amygdala, hippocampus, anterior cingulate and this activation in REM may play a role in emotional aspects of dreams in animals.

Further understanding of sleep substrates requires development of animal models of sleep. Fruit fly, zebra fish and animal models with genetic alterations (e.g knock out mice models) are beginning to provide insights into sleep mechanisms.

Sleep disorders:
There is immense progress in this area that includes- identification of new sleep disorders, better understanding of the previously known sleep disorders, newer treatments of sleep disorders. Catathrenia or nocturnal groaning is a new parasomnia that presents with clusters of groaning during stage-II non-REM sleep and REM sleep. These patients have normal neurological and ENT examination. Rhythmic foot movements while falling asleep that may continue into light sleep is another newly described sleep disorder. A major susceptibility locus on chromosome 12q has been identified in patients with restless leg syndrome (RLS). These patients may also have decreased iron content in the brain. Dopaminergic agonists are proving to be effective therapy for treatment of RLS.

REM behavior disorder (RBD) consists of abnormal behaviors during REM sleep due to lack of muscular atonia that typically accompanies REM. Decreased striatal dopaminergic innervation and decreased striatal dopaminergic transporter in idiopathic RBD have recently been reported.

Insomnia is the commonest sleep disorder which still needs to be better understood for its neural substrates. Recent descriptions of fatal familial insomnia have provided further insights into the role of thalamus in sleep and neurodegenerative conditions with persistent insomnia as a key feature. Further studies are being done to understand the role of melatonin in treatment of insomnia in children and adults. Newer treatments of insomnia with more selective agents have recently been approved that include Zolpidem and Zaleplon. Further studies of effective therapeutic agents including longer acting versions of approved agents are being conducted.

Newer treatments of hypersomnias have emerged. These include selective wake promoting agent such as modafinil and sodium oxybate for treatment of cataplexy. Obstructive Sleep apnea (OSA) is now being recognized as associated with hypertension and attendant cardiovascular morbidity and mortality. Role of sleep apnea in Stroke is being identified. OSA is also associated with insulin resistance in obese and non-obese individuals. Association between sleep apnea and Apo-E4 has been noted. At the therapy end, newer and smarter CPAP systems with better fitting masks and headgear are translating into direct improvements in patient care.

Sleep and aging is another emerging discipline. Changes in sleep patterns may occur as an association of aging. These may include- fragmented sleep, advanced sleep phase shift and more daytime napping. Primary sleep disorders may occur with increased frequency with age (e.g PLMS, sleep apnea)- and - medical, neurological, psychiatric disorders may lead to sleep disorders in the elderly e.g Parkinson's disease and dementias. Hypersomnia in elderly tends to be associated with cognitive decline and dementia. Insomnia does not tend to be associated with cognitive decline.

Sleep and public health:
Optimal sleep is key to the health of a society and lack of sleep has significant public health implications. 4% of all fatal crashes in US occur due to drowsy drivers (NHTSA). Untreated hypersomnia, <6 hours of sleep, shift work, commercial truck driving and late night or early morning driving are important risk factors. There is recent recognition of medical errors due to fatigue and sleepiness in resident physicians. There are suggestions of work place accidents possibly related to fatigue and sleepiness. Discovery of electricity and light bulb and now availability of round the clock television programs has lead to 24 hour activities and entertainment. The impact of this societal sleep loss may be significant.

Future directions:
Despite the many advances in last several years, sleep medicine is still in its infancy. We need to develop new animal models of sleep to better understand the neurobiological substrates of sleep and sleep loss. Longitudinal epidemiological studies are needed to better understand the changes in sleep with age. We need to understand the effects of sleep loss and the significance of rest and sleep recovery. Twin studies of sleep disorders need to be done. Very limited data is there on autopsy studies of brain in sleep disorders. This needs to be done as a multi-center effort as in Alzheimer's disease. Long-term safety and efficacy studies of psycho-stimulants and hypnotics need to be done. We know little about sleep patterns in various neurological disorders e.g autism, neurodegenerative conditions. We also need to develop better tools to study sleep. Current methods are cumbersome and expensive. We also need to understand sleep across the cultural and national boundaries.

Last but not the least, we need to develop a clear strategy for education and training in sleep. This includes education of physicians, patients, health care personnel and public education. The educational endeavors have to be global to be successful in full sense of the word. The spectrum of education should include sleep and sleep disorders but also attitudes regarding the significance of sleep. Quality of sleep is intricately tied to quality of life.

While much more needs to be learnt regarding sleep, it remains a distinct brain state and neurologist and neuroscientists along with specialists in other areas (including dentistry, otolaryngology, psychiatry, psychology, pulmonary medicine) need to play key role in the further understanding of sleep and sleep disorders and should be on the forefronts of providing care to patients with sleep disorders.

References:
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