Review Article

Indian J Med Res 131, February 2010, pp 126-140

Overview of sleep & sleep disorders

S. Chokroverty

Department of Neuroscience, Divisions of Sleep Medicine & Clinical Neurophysiology at the NJ Neuroscience Institute at JFK Medical Center, Edison, NJ & Seton Hall University, South Orange, NJ & Department of Neurology at Robert Wood Johnson Medical School, New Brunswick, NJ, USA

Received February 5, 2009

Sleep is defined on the basis of behavioural and physiological criteria dividing it into two states: non rapid eye movement (NREM) sleep which is subdivided into three stages (N1, N2, N3); and rapid eye movement (REM) sleep characterized by rapid eye movements, muscle atonia and desynchronized EEG. Circadian rhythm of sleep-wakefulness is controlled by the master clock located in the suprachiasmatic nuclei of the hypothalamus. The neuroanatomical substrates of the NREM sleep are located principally in the ventrolateral preoptic nucleus of the hypothalamus and those of REM sleep are located in pons. A variety of significant physiological changes occur in all body systems and organs during sleep as a result of functional alterations in the autonomic and somatic nervous systems. The international classification of sleep disorders (ICSD, ed 2) lists eight categories of sleep disorders along with appendix A and appendix B. The four major sleep complaints include excessive daytime sleepiness, insomnia, abnormal movements or behaviour during sleep and inability to sleep at the desired time. The most important step in assessing a patient with a sleep complaint is obtaining a detailed history including family and previous histories, medical, psychiatric, neurological, drug, alcohol and substance abuse disorders. Some important laboratory tests for investigating sleep disorders consist of an overnight polysomnography, multiple sleep latency and maintenance of wakefulness tests as well as actigraphy. General physicians should have a basic knowledge of the salient clinical features of common sleep disorders, such as insomnia, obstructive sleep apnoea syndrome, narcolepsy-cataplexy syndrome, circadian rhythm sleep disorders (*e.g.*, jet leg, shift work disorder, *etc.*) and parasomnias (*e.g.*, partial arousal disorders, REM behaviour disorder, *etc.*) and these are briefly described in this chapter. The principle of treatment of sleep disorders is first to find cause of the sleep disturbance and vigorously treat the co-morbid conditions causing the sleep disturbance. If a satisfactory treatment is not available for the primary condition or does not resolve the problem, the treatment should be directed at the specific sleep disturbance. Most sleep disorders, once diagnosed, can be managed with limited consultations. The treatment of primary sleep disorders, however, is best handled by a sleep specialist. An overview of sleep and sleep disorders *viz.*, Basic science; international classification and approach; and phenomenology of common sleep disorders are presented.

Key words Arousals - dreams - insomnia - narcolepsy - OSAS - parasomnia - REM sleep - sleep - sleep-wake rhythm

DEFINITION OF SLEEP, SLEEP ARCHITECTURE AND SLEEP PROFILES

From a scientific standpoint, sleep is defined on the basis of both the behaviour of the person while asleep and related physiological changes (Table I) that occur to the waking brain's electrical rhythms in sleep[1]. The behavioural criteria consist of a lack of mobility or slight mobility, slow eye movements, characteristic specifies-specific sleeping posture, reduced response to external stimulation, increased reaction time, elevated arousal threshold, an impaired cognitive function and a reversible unconscious state. The physiological criteria are based on the findings of EEG, electro-oculography (EOG) and electromyography (EMG). It is important to differentiate sleepiness from fatigue. Fatigue, however, can be a secondary consequence of sleepiness. The moment of sleep onset is characterized by gradual changes in many behavioural and physiological characteristics.

Based on three physiological measurements (EEG, EOG and EMG), sleep is divided into two states with independent functions and controls: non rapid eye movement (NREM) and REM sleep alternating in a cyclic manner (total of 4 to 6 cycles are noted during sleep in adults), each cycle lasts on an average from 90 to 110 min. In adult human, the first third of sleep is dominated by the slow-wave sleep and the last third is dominated by REM sleep. NREM sleep accounts for 75 to 80 per cent of sleep time in adult humans and is subdivided into 4 stages (NREM stages 1 to 4) according to the traditional Rechtschaffen and Kales (R-K)[2] scoring manual. But according to the recent American Academy of Sleep Medicine (AASM) scoring manual[3], this is subdivided into 3 stages (N1, N2, N3) mainly on the basis of EEG criteria.

REM sleep accounts for 20 to 25 per cent of total sleep time. The EEG tracings during REM sleep are characterized by fast rhythms and theta waves, some of which may have a saw-tooth appearance (Fig.). The hallmark of REM sleep is the presence of rapid eye movements in all directions and the marked diminution or absence of muscle activities in the chin EMG. In addition to phasic rapid eye movements in all directions, there are also phasic swings in blood pressure and heart rate, irregular respiration and phasic tongue movements. A few periods of apnoea or hypopnoea may arise during REM sleep.Thus in the normal adult, there is an orderly progression from wakefulness to sleep onset to NREM and then to REM sleep. NREM sleep is characterized by progressively decreased responsiveness to external stimulation accompanied by slow eye movements followed by EEG slow wave activity associated with spindles and K complexes and decreased muscle tone. REM sleep is characterized by rapid eye movements, further reduction of responsiveness to stimulation, absent muscle tone and low voltage fast EEG activities mixed with distinctive saw-tooth waves.

Evolution of sleep patterns across the lifespan

Evolution of EEG and sleep states from the foetus, pre-term and term infant, early childhood, adolescence to adulthood follows in an orderly manner depending on the maturation of the central nervous system[1]. Such ontogenetic changes will be significantly affected by neurological, environmental and genetic factors as well as co-morbid medical or neurological disorders. Sleep requirements change dramatically from infancy to old age. Newborns have a polyphasic sleep pattern with a total of 16 h of sleep per day. By the time a child is 3 to 5 yr of age, the sleep requirement falls to approximately 11 h per day and sleep requirement for an adolescent of 9 to 10 yr age is approximately

Table I. Behavioural and physiological criteria of wakefulness and sleep

Criteria	Awake	Non–rapid eye movement sleep	Rapid eye movement sleep
Posture	Erect, sitting, or recumbent	Recumbent	Recumbent
Mobility	Normal	Slightly reduced or immobile; postural shifts	Moderately reduced or immobile; myoclonic jerks
Response to stimulation	Normal	Mildly to moderately reduced	Moderately reduced to no response
Level of alertness	Alert	Unconscious but reversible	Unconscious but reversible
Eyelids	Open	Closed	Closed
Eye movements	Waking eye movements	Slow rolling eye movements	Rapid eye movements
Electroencephalography	Alpha waves; desynchronized	Synchronized	Theta or saw tooth waves; desynchronized
Electromyography (muscle tone)	Normal	Mildly reduced	Moderately to severely reduced or absent
Electro-oculography	Waking eye movements	Slow rolling eye movements	Rapid eye movements

Source: Ref. 1 (Reprinted with permission)

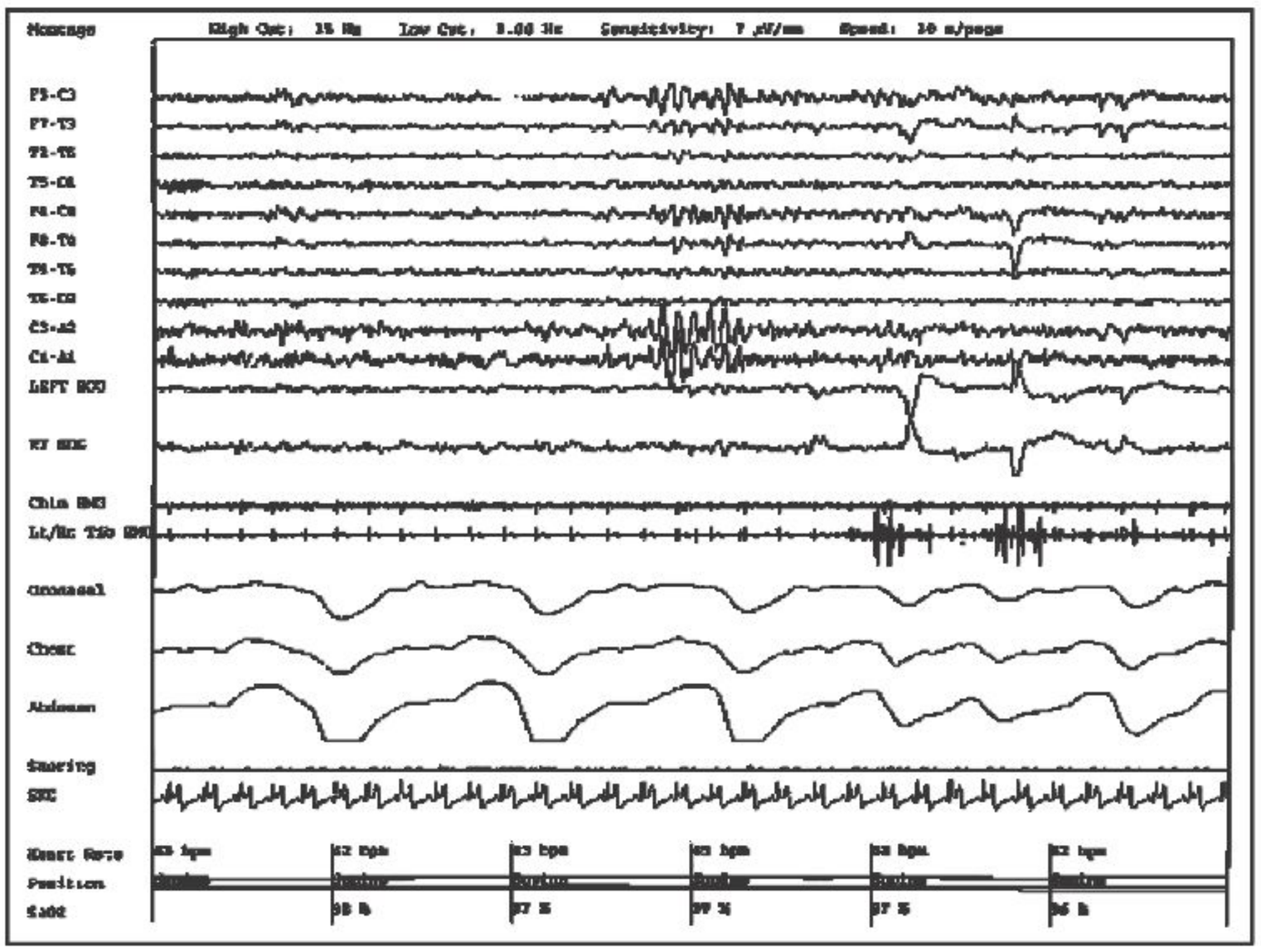

Fig. Polysomnographic recording showing rapid eye movement (REM) sleep. Electroencephalograms (top 10 channels) show mixed frequency theta, some alpha, and low-amplitude beta activities intermixed with sawtooth waves (middle of the recording), seen prominently in C3-A2 and C4-A1 derivations. Rapid eye movements are seen in electro-oculographic channels. Chin electromyogram shows marked hypotonia, whereas tibialis electromyogram shows phasic myoclonic bursts.
Source: Ref. 1 (Reproduced with permission).

10 h per day. In preschool children, sleep assumes a biphasic pattern. Adults exhibit a monophasic sleep pattern, with an average duration of 7.5 to 8 h per night, but the pattern reverts to biphasic in elderly people. In newborn infants, the amount of sleep time spent in the REM state is about 50 per cent but by about 6 yr of age, REM has decreased to the normal adult pattern of 25 per cent. By 3 months of age, the NREM/REM cycling pattern of adult sleep is established.

Circadian neurobiology and sleep-wake rhythms

The human circadian timing system functions to co-ordinate humoral, physiological and behavioural mechanisms to promote sleep and waking behaviour. Regulation of sleep-wakefulness is modulated by two opposing factors, homeostatic drive for sleep and circadian rhythm promoting arousal. The homeostatic factor refers to an increased propensity for sleepiness with longer periods of prior wakefulness whereas the circadian factor refers to variations in physiological alertness and sleepiness (timing, duration and other characteristics) that vary cyclically with time of day. In the morning after awakening, the homeostatic drive for sleep is virtually nil and supra chiasmatic nuclei (SCN) output is low as shown by the intracerebral recording of neuronal firing rate. Homeostatic drive gradually increases as the day progresses and is countered by an increasing SCN output. At the end of the day, however, SCN output decreases and now homeostatic drive results in the onset of sleep. Early in the morning, homeostatic drive is diminished and circadian arousal influences result in awakening. There are two very highly vulnerable periods of sleepiness: 0200 to 0600 h and 1400 to 1800 h. The former is stronger than the latter. The highest number of sleep related accidents has been observed during this period.

Cytokines and immune system

Cytokines are proteins produced by leukocytes and other cells functioning as intracerebral mediators that may play an important role in immune and sleep regulation[1]. Several cytokines (*e.g.,* interleukin or IL, interferon alpha or IF-α and tumour necrosis factor or TNF) have been shown to promote sleep. There are however, other sleep-promoting substances called sleep factors which increase in concentration during prolonged wakefulness or during infection and enhancing sleep. These factors include delta sleep-

inducing peptides, muramyl peptides, cholecystokinin, arginine vasotocin, vasoactive intestinal peptide, growth hormone-releasing hormone (GHRH), somatostatin, prostaglandin D_2, and adenosine. There is evidence that cytokines play an important role in the pathogenesis of excessive daytime sleepiness (EDS) in a variety of sleep disorders and in sleep deprivation. Increased production of pro-inflammatory cytokines (IL-6 and TNF-α) have been noted during sleep deprivation causing excessive sleepiness. Viral or bacterial infections causing EDS and increased NREM sleep are associated with increased production of TNF-α and IL-B). Increased sleepiness and disturbed sleep in other inflammatory disorders such as HIV infection and rheumatoid arthritis are associated with increased amounts of circulating TNF-α. Several authors suggested that excessive sleepiness in obstructive sleep apnoea syndrome, narcolepsy, insomnia or idiopathic hypersomnia may be mediated by cytokines such as IL-6, TNF-α [4].

Sleep and dreams

It is believed that approximately 80 per cent of dreams occur during REM sleep and 20 per cent occur during NREM sleep. It is easier to recall REM dreams than NREM dreams. It is also easier to recall dreams if an individual is awakened immediately after the onset of REM dreams, rather than trying to remember them the next morning upon getting out of bed. REM dreams are often vivid, unrealistic and bizarre. In contrast, dream recall, which sometimes may partially occur upon awakening immediately from the NREM dream state, is more realistic. Most of our dreams take place in natural colour, rather than black and white. In our dreams, we employ all five senses. In general, we use mostly our visual sensations, followed by auditory sensations, tactile, smell, and taste sensations are represented least. Some people have frequent, frightening dreams called nightmares or dream anxiety attacks, which appear to arise from intense, anxiety-provoking incidents in the dreamer's life. Nightmares are very common in children, beginning around the age of three to five years. Nightmares decrease in old age. Sometimes in fearful dreams, the individual may enact past stressful events (for example, a scene in a battle field or a car accident). The neurobiological significance of dreams remains unknown. Dream enacting behaviour associated with abnormal movements during sleep constitutes an important REM parasomnia called REM sleep behaviour disorder.

Functional neuroanatomy of sleep

The neuroanatomical substrates of REM and NREM sleep and wakefulness are located in separate parts of the central nervous system[5]. There are no discrete sleep-wake promoting centers but these states are produced by changes in the interconnecting neuronal systems modulated by neurotransmitters and neuromodulators. The methods employed to characterize sleep-wake generator sites included lesion, stimulation, ablation, intracellular recording, C-fos immunoreactivity (*C-FOS* or immediate early gene is a nuclear protein released during activation of neurons) and neuroimaging mapping of neuronal networks[6].

To explain the mechanism of REM sleep there are three animal models available[5]. The earliest and most generally well known is the McCarley-Hobson reciprocal interaction model based on reciprocal interaction of REM-on and REM-off neurons[6]. In the model proposed by Luppi's group[7] active neurons during REM sleep are identified in a small area in the dorsolateral pontine tagmentum called sublaterodorsal (SLD) nucleus in the rats (corresponding to dorsal sub-coeruleus or perilocus coeruleus alpha region in cats). The onset of REM sleep is thought to be due to activation of REM-on glutamatergic neurons from the SLD. During NREM sleep and wakefulness these neurons in the SLD would be inhibited (hyper-polarized) by tonic GABA-ergic input from GABA-ergic REM-off neurons located in the SLD, deep mesencephalic and pontine reticular nuclei, and ventrolateral peri-aqueductal gray (VlPAG) as well as by monoaminergic REM-off neurons. In the Luppi model[7], therefore, GABA-ergic neurons and glutamatergic neurons play a crucial role in REM generation. GABA-ergic neurons are also responsible for inactivation of monoaminergic neurons during REM sleep and cholinergic neurons do not play a crucial role in activating REM executive neurons in this model. In the third model proposed by Lu and co-workers[8], there is a flip-flop switch interaction between GABA-ergic REM-off neurons in deep mesencephalatic (DM), ventrolateral peri-aqueductal gray (VLPAG) and lateral pontine tagmentum (LPT) and GABA-ergic REM-on neurons in SLD, and a dorsal extension of SLD named the precoeruleus (PC). These mutually inhibitory neuronal populations (SLD GABA-ergic REM-on and GABA-ergic REM-off neurons in the DM-LPT) serve as flip-flop switch.

Neuroanatomical substrates of NREM sleep

Neurophysiologic studies of sleep really began after astute clinicopathologic observations by von

Economo, who examined patients with encephalitis lethargica at the beginning of the twentieth century[9,10]. It was noted that lesions of encephalitis lethargica, which severely affected the posterior hypothalamic area, were associated with the clinical manifestation of extreme somnolence whereas morphologic alterations in the anterior hypothalamic region were associated with sleeplessness. These observations led scientists to believe in the existence of the so-called sleep-wake centers[5,10-13].

The active hypnogenic neurons for NREM sleep are thought to be located in two regions[5]: (*i*) the region of the nucleus tractus solitarius (NTS) in the medulla, and (*ii*) the preoptic area of the hypothalamus and the basal forebrain area. The evidence is based on stimulation, lesion, and ablation studies, as well as extracellular and intercellular recordings[5]. The active inhibitory role of the lower brain stem hypnogenic neurons on the upper brain stem ascending reticular activating systems has been clearly demonstrated by Batini's[14,15] experiment of midpontine pretrigeminal section. Similarly, electrical[16] stimulation of the preoptic area, which produced EEG synchronization and behavioural state of sleep, supported the idea of the existence of active hypnogenic neurons in the preoptic area[6]. Nauta's[12] experiments in 1946 that showed insomnia after lesions of the preoptic region also supported the hypothesis of active hypnogenic neurons in the forebrain preoptic area. Later experiments by McGinty and Sterman[17] in 1968 confirmed Nauta's observations. More recently, ibotenic lesions in the preoptic region have been found to produce insomnia, and these results support the active hypnogenic role of preoptic area[6,18]. In the same experiments, however, injections of muscimol (a GABA agonist) in the posterior hypothalamus transiently recovered sleep, suggesting that the sleep-promoting role of the anterior hypothalamus is dependent on inhibition of posterior hypothalamic histaminergic awakening neurons. It should also be emphasized that in 1934 Dikshit[19] induced sleep by intrahypothalamic injection of acetylcholine suggesting the presence of sleep center in the hypothalamus. The contemporary theory suggests that NREM sleep promoting neurons are thought to be found in the VLPO area of the anterior hypothalamus as well as in the region of the NTS in the medulla.

The contemporary theory for the mechanism of NREM sleep thus suggests a reciprocal interaction between two antagonistic neurons in the VLPO of the anterior hypothalamus and wake-promoting neurons in the tuberomammillary nuclei of the posterior hypothalamus, as well as locus coeruleus, dorsal raphe, basal forebrain and mesopontine tagmentum[6,20]. Reciprocal interaction between sleep promoting neurons in the regions of the NTS and wake-promoting neurons within the ARAS of the brainstem independently of the reciprocal interaction of the neurons of the forebrain also plays a role in the generation of NREM sleep.

There are many important unanswered questions remaining regarding the mechanism of sleep. Why do VLPO neurons fire at sleep onset? What initiates cascade of dysfacilitation in the brainstem wake-promoting neurons? What initiates activation of LDT-PPT neurons at REM onset? What causes activation of GABA-ergic pontine neurons at the onset of REM sleep? What causes activation of wake-promoting neurons at sleep offset? And, finally, what maintains NREM-REM cycling?

Physiological changes in sleep

A variety of physiological and behavioural changes occur during normal wakefulness, NREM and REM sleep[21] (Table II). These changes are most commonly noted in the somatic and autonomic nervous system (ANS); in the respiratory, cardiovascular and gastrointestinal systems; in endocrine, renal and sexual functions; and in thermoregulation. An increase in the parasympathetic tone and a decrease in sympathetic activity during NREM sleep with further increase of parasympathetic tone and a decrease in sympathetic activity during REM sleep constitute fundamental ANS changes. During REM sleep, however, sympathetic activity increases intermittently. Sympathetic nerve activity in muscle and the vascular bed of the skin as measured by microneurographic technique is reduced during NREM sleep but is increased during REM sleep.

The respiratory neurons in the ponto-medullary region show a decreased firing rate during both NREM and REM sleep. Muscle tone in the upper airway decreases slightly in NREM sleep and decreases markedly and disappears in REM sleep, resulting in an increase in upper airway resistance. During NREM sleep, hypercapnic and hypoxic ventilatory responses are moderately reduced but are more markedly decreased during REM sleep. Tidal volume and alveolar ventilation decrease during sleep; arterial oxygen tension is mildly decreased and arterial carbon dioxide tension is slightly increased during both NREM and REM sleep. Thus, respiration is vulnerable during

Table II. Physiological changes during wakefulness, NREM sleep, and REM sleep

Physiology	Wakefulness	NREM sleep	REM sleep
Parasympathetic activity	++	+++	++++
Sympathetic activity	++	+	Decreases or variable (++)
Heart rate	Normal sinus rhythm	Bradycardia	Bradytachyarrhythmia
Blood pressure	Normal	Decreases	Variable
Cardiac output	Normal	Decreases	Decreases further
Peripheral vascular resistance	Normal	Normal or decreases slightly	Decreases further
Respiratory rate	Normal	Decreases	Variable; apnoeas may occur
Alveolar ventilation	Normal	Decreases	Decreases further
Upper airway muscle tone	++	+	Decreases or absent
Upper airway resistance	++	+++	++++
Hypoxic and hypercapnic ventilatory responses	Normal	Decreases	Decreases further
Cerebral blood flow	++	±	++++
Thermoregulation	++	+	—
Gastric acid secretion	Normal	Variable	Variable
Gastric motility	Normal	Decreases	Decreases
Swallowing	Normal	Decreases	Decreases
Salivary flow	Normal	Decreases	Decreases
Migrating motor complex (a special type of intestinal motor activity)	Normal	Slow velocity	Slow velocity
Penile or clitoral tumescence	Normal	Normal	Markedly increased

NREM, non-rapid eye movement; REM, rapid eye movement; +, mild; ++, moderate; +++, marked; ++++, very marked; –, absent; ±, decreased. Any increment is designated by plus sign.
Source: Ref. 21 (Reproduced with permission)

normal sleep and a few periods of apnoeas may occur, especially at the onset of sleep and during REM sleep. Sleep related alveolar hypoventilation and increased upper airway resistance may predispose susceptible individuals to upper airway occlusion and obstructive apnoea. Patients with neuromuscular disorders, chronic obstructive pulmonary disease and bronchial asthma may be affected adversely from such hypoventilation. Asthmatic attacks may be exacerbated at night as a result of broncho-constriction during sleep[22].

Heart rate, blood pressure, cardiac output, and peripheral vascular resistance decrease during NREM sleep and decrease still further during REM sleep. Cerebral blood flow and cerebral metabolic rates for glucose and oxygen decrease during NREM sleep but increase to above waking values during REM sleep. Thus profound haemodynamic changes (unstable blood pressure and heart rate, progressive decrease in cardiac output causing maximum oxygen desaturation and periodic breathing and intermittent increase of sympathetic activity during REM sleep) may explain increasing mortality during the early morning hours, especially in patients with cardiopulmonary disease. These hemodynamic and sympathetic alterations may initiate increased platelet aggregations, plaque rupture and coronary arterial spasm which may trigger thrombotic events that cause myocardial infarction, ventricular arrhythmia, and even sudden cardiac death and stroke[23,24].

Growth hormone secretions exhibit a pulsatile increase during NREM sleep in the first third of the normal sleep period. Prolactin secretion also rises 30 to 90 min after the onset of sleep. Sleep inhibits cortisol secretion. Thyroid stimulating hormones secretion reaches a peak in the evening and then decreases throughout the night. Testosterone levels in men increase during sleep rising from trough levels at 2000 h to peak levels at 0800 h, but no clear relation has been demonstrated between the levels of gonadotrophic hormones and the sleep-wake cycle in children or adults. Melatonin which is released by the pineal gland attains its highest secretion levels between 0300 h and 0500 h, then decreases to low levels during the day. Body temperature begins to fall at the onset of sleep and reaches its lowest point during the third sleep cycle. Thermoregulation is maintained during NREM

sleep but is non existent in REM sleep. Penile erection and clitoral tumescence occur during REM sleep.

The functions of sleep

The biological function of sleep remains the greatest mystery of all times, although it is known that sleep is essential and that sleep deprivation, either resulting from lifestyle or sleep disorders (*e.g.*, sleep apnoea, insomnia, medical, psychological, psychiatric, medication-related or neurological diseases) will cause short-term and long-term consequences[25]. Short-term effect leads to impaired attention and concentration, impaired quality of life, increased rates of absenteeism with reduced productivity and accidents at work, home or on the road. Long-term consequences of sleep deprivation include increased morbidity and mortality from increasing automobile accidents, coronary artery disease, heart failure, high blood pressure, obesity, type 2 diabetes mellitus, stroke and memory impairment as well as depression. Long-term consequences, however, remain controversial. Sleep is thought to be restorative, conservative, adaptive, thermoregulatory and memory consolidative functions. Walker's group[26] concluded after sleep deprivation experiments that sleep before learning is critical for human memory consolidation. In contrast to all these studies, Vertes and Siegel[27] took the opposite position contending that REM sleep is not involved in memory consolidation, at least not in humans, citing several lines of evidence. The strongest evidence cited by them include examples of individuals with brain stem lesion with elimination of REM sleep or those on antidepressant medications suppressing REM sleep exhibiting no apparent cognitive deficits. They concluded that REM sleep is not involved in declarative memory and REM sleep is not critical for cognitive processing and sleep. Whether NREM is important for declarative memory also remains somewhat contentious.

APPROACH TO THE PATIENT WITH SLEEP COMPLAINTS

Several epidemiological studies have clearly shown that sleep complaints are very common in the general population[28]. According to the report of the National Center of Sleep Disorders Research[29], more than 40 million people in the United States suffer from chronic disorders of sleep and wakefulness. About 35 per cent of the population has difficulty falling asleep, maintaining sleep, early morning awakening, or non-restorative sleep and in 10 per cent this insomnia is a persistent problem interfering with daytime function. Sleep apnoea affects 3 to 4 per cent of the population which is translated into millions of individuals. In terms of excessive daytime sleepiness in a population based study, Young[30] reported daytime sleepiness in 1 in 5 adults. Some important epidemiological factors which emerged in various studies include old age, female gender, poor education and socio-economic status, recent stress, depression, anxiety, alcohol, drug abuse or physical disease. It is important for physicians to be aware of this high prevalence of sleep disturbance which causes considerable physical and psychological stress.

The four major sleep related complaints for which patients seek medical attention are excessive daytime somnolence (EDS), insomnia, abnormal movements or behaviours during sleep, and an inability to sleep at the desired time. Insomnia patients may complain of some or all of the following: difficulty initiating or maintaining sleep, repeated awakenings or early morning awakenings, non-restorative sleep, daytime fatigue, lack of concentration, irritability, anxiety, depression, and muscle aches and pains. Insomnia may be primary (no causes found) or co-morbid with other conditions. Patients with hypersomnia may complain of EDS, a lack of relief of symptoms after additional nighttime sleep, inability to concentrate and impaired cognition and motor skills. The most common cause of EDS is behaviourally-induced insufficient sleep syndrome. An approach to a patient with sleep complaints must begin with a comprehensive knowledge of the disorder listed in the latest edition of the International Classification of Sleep Disorders (ICSD-2)[31] so that the patient can be evaluated in the proper manner, paying particular attention to the history and physical findings before ordering laboratory tests. The ICSD-2 lists 8 broad categories of disorders of sleep along with several subcategories under each category as well as appendices A and B.

Method of clinical evaluation

The first step in assessing a patient with a sleep disturbance must be clinical based on history and physical examination before laboratory tests are undertaken[28]. The history should include details about sleep habits; history of current or previous medical, neurological and psychiatric illnesses; drug and alcohol consumption as well as family history. The entire 24 h span must be included in brief history and not just symptoms occurring at sleep onset or during sleep at night. Particular attention should

be paid to the frequency, type and time of onset of the symptoms. Arousal disorders, REM behaviour disorder (RBD), and sleep-wake transition disorders are present at the particular time during the night or during certain stages of sleep. Symptoms occurring in the early evening when the patient is lying in bed or at sleep onset may suggest a diagnosis of restless legs syndrome (RLS). Repeated awakenings throughout the night, snoring and cessation of breathing during sleep may suggest a diagnosis of obstructive sleep apnoea syndrome (OSAS). EDS and daytime fatigue may also suggest a diagnosis of OSAS. Additionally, excessive sleepiness in the daytime and irresistible desire to fall asleep and the feeling of being refreshed following daytime sleep are characteristic symptoms of narcolepsy. If the patient presents with abnormal movements and behaviour during the first third of the night, a diagnosis of partial arousal disorder (sleep walking, sleep terror, confusional arousal) is strongly suggested. In contrast, the occurrence of complex motor activities and behaviour with or without injury to self or the bed partner during the middle and later part of the night will suggest a diagnosis of RBD. Leg jerks throughout the night may suggest periodic limb movements in sleep (PLMS). It is important to conduct an interview with the patient's bed partner or care giver (or parent in case of a child) for diagnosis of abnormal movements and behaviour as well as breathing disorders during sleep. The bed partner may also be in a position to answer questions about the patient's sleeping habits, history of drug use, history of stress at home, work or school and changes in sleep habits. Completing a sleep questionnaire or keeping a sleep log or diary over a 2 wk period may give important indications of sleep habits and sleep hygiene. Family history may be important in certain sleep disorders such as narcolepsy, RLS, OSAS and partial arousal disorders. History must be followed by careful physical examination to document evidence of various medical disorders such as respiratory, cardiovascular, endocrinological or neurological disorders, especially those that affect the brain stem region or the neuromuscular system. Examination may also uncover upper airway anatomical abnormalities, which are noted in many cases with OSAS. There are also several scales available to assess subjective degree of sleepiness, such as Stanford Sleepiness Scale, Visual Analogue Scale and Epworth Sleepiness Scale[25]. Laboratory assessment follows history and physical examination and is described below.

Laboratory studies: Laboratory assessment must be considered an extension of the history and physical examination[28]. Laboratory tests should include a diagnostic work up for the primary condition causing secondary or co-morbid sleep disturbance and the work up for the sleep disturbance itself (Table III). The two most important laboratory tests are an overnight polysomnography (PSG) and multiple sleep latency test (MSLT). All night PSG studies simultaneously record several physiological variables (EEG, EMG, EOG, EKG, airflow at the nose and mouth, respiratory effort and oxygen saturation) and are important in confirming the diagnosis of OSAS as well as documenting the severity of sleep apnoea, hypoxaemia and sleep fragmentation. The PSG recording should also include body position monitoring and snoring recording. Overnight PSG determines an optimal pressure for continuous positive airway pressure (CPAP) – a treatment for OSAS – and is also helpful in supporting the diagnosis of narcolepsy and the parasomnias. Overnight PSG with simultaneous video recording can confirm REM sleep behaviour

Table III. Laboratory tests to assess sleep disorder

▪ Diagnostic workup for the primary or co-morbid condition causing sleep disturbance
▪ Laboratory tests for the diagnosis and monitoring of sleep disorders
▪ Overnight polysomnography (PSG)
▪ Multiple sleep latency tests (MSLT)
▪ Maintenance of wakefulness test
▪ Actigraphy
▪ Video-PSG
▪ Standard electroencephalography (EEG) and video-EEG monitoring for suspected seizure disorders
▪ Imaging studies
▪ Upper airway imaging for obstructive sleep apnoea syndrome
▪ Neuroimaging studies (*e.g.*, computed tomography, magnetic resonance imaging) and cerebral angiography in cases of suspected neurological illness causing sleep disorder
▪ Positron emission tomography and single-photon emission computed tomography in special situations
▪ Miscellaneous tests
▪ Pulmonary function tests in cases of suspected bronchopulmonary and neuromuscular disorders causing sleep-disordered breathing
▪ Histocompatibility leukocyte antigen for suspected narcolepsy
▪ Cerebrospinal fluid hypocreatin 1 levels in suspected narcolepsy
▪ Serum iron and ferritin levels for patients with restless legs syndrome
▪ Electromyography (EMG) and nerve conduction studies to exclude co-morbid or secondary restless legs syndrome

disorder and is particularly useful for the documentation of unusual movements and behaviours during the night time sleep in patients with parasomnias and nocturnal seizures.

The MSLT is essential in documenting pathological sleepiness (*e.g.*, sleep onset latency of less than 8 min) and when diagnosing narcolepsy. The presence of two sleep onset REMs in four or five nap studies and sleep onset latency of less than 8 min strongly suggests a diagnosis of narcolepsy.

The maintenance of wakefulness test (MWT) is a variant of MSLT measuring for subject's ability to stay awake. It also consists of 4 to 5 trials of remaining awake occurring every 2 h. Each trial is terminated if no sleep occurs after 40 min or immediately after the first 3 consecutive epochs of stage 1 NREM sleep or the first epoch of any other stage of sleep. If the mean sleep latency is less than 8 min, it is then considered an abnormal test. The MWT is less sensitive than the MSLT as a diagnostic test for narcolepsy but is more sensitive in assessing the effect of treatment (*e.g.*, CPAP titration in OSAS and stimulant therapy in narcolepsy). Another important laboratory test for assessing sleep disorders is actigraphy. This technique utilizes an actigraph worn on the wrist or ankle to record acceleration or deceleration of body movements which indirectly indicates sleep-wakefulness. Actigraphy for days or weeks is a useful laboratory test in patients with insomnia and circadian rhythm sleep disorders as well as in some patients with prolonged daytime sleepiness. Magnetic resonance imaging study and other neuroimaging techniques should be performed to exclude structural neurological lesions. Appropriate laboratory tests including pulmonary function studies should also be performed to exclude any suspected medical disorders that may be the cause of the patient's insomnia or hypersomnia.

CLINICAL PHENOMENOLOGY

Obstructive sleep apnoea syndrome (OSAS)

Based on the definition of at least five apnoeas or hypopnoeas per hour of sleep accompanied by EDS[3], the prevalence of OSA is 4 per cent in men and 2 per cent in women between ages 30 and 60. There is a strong association between OSAS and male gender, increasing age and obesity. The condition is common in men older than age 40 and among women incidence of OSAS is greater after menopause. Approximately 85 per cent of patients with OSAS are men and obesity is present in about 70 per cent of OSAS patients[31].

The symptoms of OSAS can be divided into two groups; those occurring during sleep and those occurring during waking hours (Table IV). Nocturnal symptoms include habitual loud snoring, choking during sleep, and cessation of breathing and abnormal motor activities during sleep (*e.g.*, shaking and jerking movements, confusional arousals or sleep-walking), severe sleep disruption, heartburn as a result of gastroesophageal reflux, nocturnal enuresis which is noted mostly in children and profuse sweating at night. The daytime symptoms include EDS which is characterized by sleep attacks lasting 0.5 to 2 h and occurring mostly when the patient is relaxing (*e.g.*, sitting down or watching television). The prolonged duration and the non-refreshing nature of the sleep attacks differentiates them from narcoleptic sleep attacks. In men, impotence is often associated with severe and long-standing cases of OSAS[32]. Physical examination may reveal obesity in approximately 70 per cent of cases, in addition to anatomic abnormalities in the upper airway. In severe cases, polycythemia and evidence of cardiac failure, pulmonary hypertension, and cardiac arrhythmias may be noted. OSA is associated with increased morbidity and mortality as a result of both short term consequences (impairment of quality of life and increasing traffic and work related accidents), and long term consequences resulting from associated and co-

Table IV. Signs and symptoms in obstructive sleep apnoea syndrome

Nocturnal symptoms during sleep:
Loud snoring (often with a long history)
Choking during sleep
Cessation of breathing (apnoeas witnessed by bed partner)
Sitting up or fighting for breath
Abnormal motor activities (*e.g.*, thrashing about in bed)
Severe sleep disruption
Gastroesophageal reflux causing heartburn
Nocturia and nocturnal enuresis (mostly in children)
Insomnia (in some patients)
Excessive nocturnal sweating (in some patients)
Daytime symptoms:
Excessive daytime somnolence
Forgetfulness
Personality changes
Decreased libido and impotence in men
Dryness of mouth on awakening
Morning headache (in some patients)
Automatic behaviour with retrograde amnesia
Hyperactivity in children
Hearing impairment (in some patients)

morbid conditions such as hypertension, heart failure, myocardial infarction, cardiac arrhythmia, stroke due to both supratentorial and infratentorial infarctions and transient ischaemic attacks as well as cognitive dysfunction, depression and insomnia. Several prospective longitudinal studies have shown a clear association between OSAS and systemic hypertension which may be noted in approximately 45 per cent of patients with OSAS[33]. In contrast, in about 30 per cent of cases of essential hypertension OSAS is noted. Several studies have shown improvement of hypertension or reduction of need for antihypertensive medications after effective treatment of OSAS with CPAP titration[32,33]. Pulmonary hypertension is noted in approximately 15 to 20 per cent of cases. Cardiac arrhythmias in the form of premature ventricular contractions, ventricular tachycardia, sinus pauses and third degree heart block as well as sudden cardiac death have been attributed to OSAS. Heart failure, mostly systolic but also diastolic heart failure (in which the studies are limited) is associated with both obstructive and central sleep apnoeas but mostly central sleep apnoeas (including Cheyne-Stokes breathing). The presence of central apnoea including Cheyne-Stokes breathing increases the mortality of patients with heart failure. Cognitive dysfunction is noted in moderately severe to severe OSAS patients but this shows improvement after satisfactory treatment with CPAP titration. There is an increasing awareness about the presence of depression and insomnia in patients with OSAS but in absence of adequate studies, the exact prevalence and impact of these conditions on OSAS cannot be determined. There is also an increased association between OSAS and metabolic syndrome (a combination of hypertension, increased insulin resistance with Type II diabetes mellitus, hypertriglyceridaemia, and obesity)[32,33].

Narcolepsy-cataplexy syndrome

The onset of narcolepsy-cataplexy in most cases is in adolescents and young adults with a peak incidence between the ages of 15 and 30. The ICSD 2[31] divides narcolepsy into three types: narcolepsy with cataplexy, narcolepsy without cataplexy and secondary narcolepsy. The major clinical manifestations of narcolepsy include narcoleptic sleep attacks (100%); cataplexy (60-70%); sleep paralysis (25-50%); hypnagogic hallucinations (20-40%); disturbed night sleep (70-80%); and automatic behaviour (20-40%). In addition to the major manifestations, patients with narcolepsy may also have four important co-morbid conditions: sleep apnoea, periodic limb movements in sleep (PLMS), REM behaviour disorder (RBD) and nocturnal eating disorder. The classic sleep attack is an irresistible desire to fall asleep in inappropriate circumstances and at inappropriate places (*e.g.*, while talking, driving, eating, playing, walking, running, working, sitting, listening to lectures, watching television or movies, during sexual intercourse, or when involved in boring or monotonous circumstances). These spells last from a few minutes to as long as 20 to 30 min and the patient generally feels refreshed upon waking. There are wide variations in frequency of attacks, anywhere from daily, weekly, monthly or every few weeks to months. Attacks generally persist throughout the patient's lifetime although fluctuations and rare temporary remissions may occur. Patients often show a decline in performance at school and work and encounter psychosocial and socio-economic difficulties as a result of sleep attacks and EDS. These sleep attacks are often accompanied by cataplexy characterized by sudden loss of tone in all voluntary muscles except respiratory and ocular muscles. The attacks are triggered by emotional factors such as laughter, rage, or anger more than 95 per cent of the time. The attacks may become either partial and are rarely unilateral. Most commonly, the patient may momentarily have head-nodding, sagging of the jaw, buckling of the knees, dropping of objects from hands, dysarthria or loss of voice, but sometimes they may slump or fall forward to the ground for a few seconds. The duration is usually a few seconds to minutes and consciousness is retained completely during the attack. Generally, cataplectic spells occur months to years after the onset sleep attacks but occasionally cataplexy is the initial manifestation. It is a life-long condition but it generally is less severe and may even disappear in old age. Rarely, status cataplecticus occurs particularly after withdrawal of anti-cataplectic medications. Sleep paralysis, hypnagogic hallucinations, disturbed night sleep and automatic behaviour are the other manifestations of narcolepsy-cataplexy syndrome. Symptomatic or secondary narcolepsy-cataplexy may result from dyencephalic and midbrain tumours, multiple sclerosis, strokes, vascular malformations, encephalitis, cerebral trauma and parapnyoplastic syndrome with anti-Ma2 antibodies may present with narcoleptic-like sleep attacks and other manifestations. Symptomatic narcolepsy is associated with cataplexy and develops in children affected with Niemann-Pick Disease Type C[31].

Idiopathic hypersomnia with or without long sleep time

Idiopathic hypersomnia closely resembles narcolepsy syndrome. This disorder is characterized

by EDS which has a presumed CNS cause but not proven and is associated with either normal (6-10 h) or prolonged (more than 10 h) nocturnal sleep documented by history, actigraphy, sleep logs or PSG. The onset of the disease is generally around the same age as narcolepsy (15 to 30 yr). The sleep pattern, however, is different from that of narcolepsy. The patient generally sleeps for hours but the sleep is not refreshing. Because of EDS, the condition may be mistaken for sleep apnoea. However, the patient does not give a history of cataplexy, snoring or repeated awakenings throughout the night. Some patients may have automatic behaviour with amnesia for the events. Physical examination uncovers no abnormal neurologic findings. This disabling and life-long condition should be differentiated from other causes of EDS. There is no clear association between idiopathic hypersomnia and HLA antigens. MSLT shows evidence of pathologic sleepiness without sleep onset REMs[31].

Insomnia

Insomnia is the most common sleep disorder affecting the population and is the most common disease encountered in the practice of sleep medicine. Insomniacs complain of difficulty initiating and maintaining sleep, including early morning awakening and non-restorative sleep occurring 3-4 times per week persisting for more than a month and associated with an impairment of daytime function. Acute insomnia may be associated with an identifiable stressful situation. Most cases of insomnia are chronic and co-morbid with other conditions which include psychiatric, medical and neurological disorders or drug and alcohol abuse[31]. In some cases, no cause is found and the condition is labelled idiopathic or primary insomnia or psychophysiological insomnia.

Restless legs syndrome

Restless legs syndrome (RLS) is the most common movement disorder but is uncommonly recognized and treated despite a lucid description of the entity in the middle of the last century. There is not a single diagnostic test for RLS and hence the diagnosis rests entirely on clinical features and is based on the International Restless Legs Syndrome Study Group (IRLSSG) criteria established first in 1995[34] and modified slightly in 2003[35]. RLS is a life-long sensory-motor neurological disorder that often begins at a very young age but is mostly diagnosed in the middle or later years. Prevalence increases with age and plateaus for some unknown reason around age 85 to 90. All 4 essential diagnostic criteria are needed to establish the diagnosis of RLS. The overall prevalence has been estimated at about 10 per cent for adult populations but the prevalence of most severe cases is approximately 2.5 per cent. In most surveys, the prevalence is greater in women than in men and the disease is chronic and progressive. Family studies of RLS suggest an increased incidence (around 40-50%) in first degree relatives of idiopathic cases. A high concordance (83%) in monozygotic twins and complex segregation analysis suggests an autosomal dominant mode of inheritance. Linkage analysis documented significant linkage to at least five different chromosomes (12Q, 14Q, 9P, 2P and 22P)[36]. Recent genome-wide association study of RLS has identified common variants in certain genomic regions conferring more than 50 per cent increase in risks to RLS[36]. These recent results linking certain genes to RLS suggest a biological basis for the condition. The sensory manifestations of RLS include intense disagreeable feelings which are described as creeping, crawling, tingling, burning, aching, cramping, knife-like or itching sensations. These sensations occur mostly between the knees and ankles causing an intense urge to move the limbs to relieve these feelings. Sometimes similar symptoms occur in arms or other parts of the body, particularly in advanced stages of the disease or when the patient develops augmentation (a hypermotor syndrome with symptoms occurring at least two hours earlier than the initial period with intensification and spreading to other body parts) resulting from long-standing dopaminergic medications. Most of the movements, especially in the early stages, are noted in the evening when the patient is resting in bed. In severe cases, movements may be noted in the daytime when the patient is sitting or lying down. At least 80 per cent of RLS patients have periodic limb movement in sleep (PLMS) and may also have periodic limb movement in wakefulness (PLMW). The condition generally has a profound impact on sleep and often the patient seeks medical attention because of sleep disturbance which is a problem of initiation although difficulty maintaining sleep also occurs because of associated PLMS.

Parasomnias

Parasomnias can be defined as abnormal movements or behaviours, including those that occur into sleep or during arousals from sleep, intermittent or episodic, or without disturbing the sleep architecture. The ICSD 2 [31] lists 15 items and some of these entities are rare. Several parasomnias may be mistaken for seizures, especially complex partial seizures and

nocturnal frontal lobe epilepsy. Somnambulism, night terror, confusional arousals, sleep enuresis, RBD and nightmares are some of the parasomnias that can be mistaken for seizures. Characteristic clinical features combined with EEG and PSG recordings are essential to differentiate these conditions.

Sleepwalking (Somnambulism)

Sleepwalking is common in children between the ages of 5 and 12. Sometimes it persists into adulthood or rarely begins in adults. Sleepwalking begins with an abrupt onset of motor activity arising out of slow wave sleep during the first 1/3 of sleep. Episodes generally last less than 10 min. There is a high incidence of positive family history. Injuries and violent activities have been reported during sleepwalking episodes but generally individuals can negotiate their way around the room. Rarely, the occurrence of homicide has been reported and sometimes abnormal sexual behaviour occurs; sleep deprivation, fatigue, concurrent illness and sedative-hypnotics are precipitating factors.

Sleep terror (Pavor nocturnus)

Sleep terror also occurs during slow wave sleep. Peak onset is between the ages of 5 and 7 yr. As with sleepwalking, there is a high incidence of family history of sleep terror. Episodes of sleep terror are characterized by intense autonomic and motor symptoms including a loud piercing scream. Patients appear highly confused and fearful. Many patients also have a history of sleepwalking episodes. Precipitating factors are similar to those described in sleepwalking.

Confusional arousals

These occur mostly before age 5 yr. As in sleepwalking and sleep terror, there is a high incidence of familial cases and the episodes arise out of slow wave sleep but occasionally may occur out of Stage 2 NREM sleep. The patient may have some automatic and inappropriate behavior, including abnormal sexual behaviour (sex-somnia or sleep sex) when the episodes occur in adults. The majority of spells are benign, but sometimes violent and homicidal episodes in adults have been described. Precipitating factors are the same as in sleepwalking or sleep terror.

Rapid eye movement sleep behaviour disorder (RBD)

RBD is an important REM sleep parasomnia commonly seen in elderly individuals. A characteristic feature of RBD is intermittent loss of REM sleep related muscle hypotonia or atonia and the appearance of various abnormal motor activities during sleep. The patient experiences violent and dream-enacting behaviour during REM sleep, often causing self-injury or injury to the bed partner. RBD may be idiopathic or secondary; most cases are now thought to be secondary and thought to be associated with neurodegenerative diseases. It is seen with increasing prevalence in patients with Parkinson's Disease (PD), multiple system atrophy (MSA), diffuse Lewy-Body disease with dementia (DLBD), corticobasal degeneration, olivopontocerebellar atrophy, and progressive supranuclear palsy (PSP). Many patients with narcolepsy, a probable degenerative disease of the hypocreatin-containing neurons in the lateral hypothalamus may also present with RBD. Some authors proposed that RBD may be an alpha-synucleinopathy disorder because alpha-synucleine inclusions have been observed in many of the associated neurodegenerative diseases (*e.g.*, PD, MSA, DLBD)[37]. RBD may precede many of these degenerative diseases. RBD may sometimes be drug induced (*e.g.*, sedative-hypnotics, tricyclic antidepressants, anticholinergics, selective serotonin reuptake inhibitors – SSRIs) or associated with alcoholism and structural brain stem lesions. RBD has been linked to dopamine dysfunction based on PET scan findings of reduced striatal pre-synaptic dopamine transporter and SPECT scan findings of reduced post-synaptic dopamine D2 receptors[38]. REM sleep without muscle atonia is the most important PSG finding. Experimentally similar behaviour has been noted after bilateral peri locus ceruleus lesions in cats[39].

Nightmares

Nightmares-intense, frightening dreams followed by awakening and vivid recall-occur during REM sleep. The most common time of occurrence, therefore, is from the middle to the late part of the night. Nightmares are typically normal phenomena. Approximately 50 per cent of children have nightmares beginning at 3-5 yr of age. The incidence of nightmares continues to decrease as one grows older and the elderly have very few or no nightmares. Nightmares are common after sudden withdrawal of REM-suppressant drugs and can also occur as side effects of certain medications, such as antiparkinsonian drugs, anticholinergics, and beta blockers.

Sleep-related eating disorders

Sleep-related eating disorders are common in women between the ages of 20 and 30 and consist of

recurrent episodes of involuntary eating and drinking during partial arousals from sleep. Sometimes the patient displays strange eating behaviour (*e.g.*, consumption of inedible or toxic substances such as frozen pizza, raw bacon and cat food). The episodes cause sleep disruption with weight gain; occasionally injury has been reported. The condition can be either idiopathic or co-morbid with other sleep disorders (*e.g.*, sleepwalking, RLS-PLMS, OSAS, irregular sleep-wake circadian rhythm disorder and use of medications such as triazolam, zolpidem and other psychotropic agents)[31]. The most common PSG findings are multiple confusional arousals with or without eating, arising predominantly from slow wave sleep, but also from other stages of NREM sleep and occasionally from REM sleep.

Catathrenia (Expiratory groaning)

This parasomnia is characterized by recurrent episodes of expiratory groaning (high-pitched, loud humming or roaring sounds) and occur in clusters, predominantly during REM sleep but may also occur during NREM sleep[40-42]. PSG findings resemble central apnoea with protracted expiratory bradypnoea without oxygen desaturation. Simultaneous audio recordings will bring out the characteristic groaning. The clinical relevance and pathophysiology of this condition remain unknown.

Sleep-related movement disorders

This new category of sleep related movement disorders is included in the ICSD 2 [31]. These movements consist of relatively simple stereotyped movements disturbing sleep. RLS, PLMS, rhythmic movement disorder, bruxism and nocturnal leg cramps are included in this category.

Rhythmic movement disorder

Rhythmic movement disorder is noted mostly in those younger than age 18 months and is occasionally associated with mental retardation. It is a sleep-wake transition disorder with three characteristic movements: head-banging, head rolling and body rocking. Rhythmic movement disorder is a benign condition and the patient outgrows the episodes.

Nocturnal leg cramps

These are intensely painful conditions accompanied by muscle tightness that occurs during sleep. The spasms usually last for a few seconds but sometimes persist for several minutes. Cramps during sleep are generally associated with awakening. Many normal individuals have nocturnal leg cramps; the cause remains unknown. Local massage or movement of the limbs usually relieves the cramps.

Bruxism (Tooth grinding)

Bruxism often presents between ages 10 and 20, but it may persist throughout life, often leading to secondary problems such as temporomandibular joint dysfunction. Both diurnal and nocturnal bruxism may be also associated with various movement and degenerative disorders such as oromandibular dystonia and Huntington's disease. It is also commonly noted in children with mental retardation or cerebral palsy. Nocturnal bruxism is noted most prominently during stages 1 and 2 NREM sleep and REM sleep. The episode is characterized by stereotypical tooth grinding and is precipitated by anxiety, stress and dental disease. Occasionally, familiar cases have been described. Local injections of botulinum toxin into masseter muscle may be used to prevent dental and temporomandibular joint complications[43].

Principles of management of sleep disorders

The principles of treatment of sleep disorder include first to find the cause of the sleep disturbance and vigorously treat the primary or co-morbid conditions causing the sleep disturbance. If a satisfactory treatment is not available for the primary condition or does not resolve the problem, then treatment should be directed at a specific sleep disturbance. It is beyond the scope of this article to discuss the management of primary sleep disorders as well as various neurological and medical diseases causing sleep disturbances.

Summary and conclusion

This review outlines an overview of sleep and sleep disorders. General physicians should have a high index of suspicion about the presence of sleep disorders which are pervasive in society. Most sleep disorders, once diagnosed, can be managed with limited consultation. The initial step is to treat any condition that may be secondarily responsible for excessive sleepiness or inability to have an adequate amount of quality sleep. However, the treatment of primary sleep disorders is best handled by a sleep specialist.

Acknowledgment

Author thanks Ms. Betty Coram for typing and Ms. Annabella Drennan for proofreading, editing and typing.

References

1. Chokroverty S. An overview of normal sleep. In: Chokroverty S, editor. *Sleep disorders medicine: Basic science, technical considerations and clinical aspects*, 3rd ed. Philadelphia: Elsevier/Butterworth; 2009.
2. Rechtschaffen A, Kales A. *A manual of standardized terminology, techniques and scoring systems for sleep stages of human subjects*. Los Angeles: UCLA Brain Information Service/Brain Research Institute; 1968.
3. *The AASM manual 2007 for the scoring of sleep and associated events. Rules, terminology and technical specifications*. Westchester, IL, USA: American Academy of Sleep Medicine; 2007.
4. Kapsimalis F, Varouchakis G, Manousaki A, Daskas S, Nikita D, Kryger M, *et al*. Cytokines and pathological sleep. *Sleep Med* 2008; *9* : 603-14.
5. Chokroverty S, Montagna P. Sleep, breathing and neurological disorders. In: Chokroverty S, editor. *Sleep disorders medicine: Basic science, technical considerations and clinical aspects*, 3rd ed. Philadelphia: Elsevier/Butterworth; 2009.
6. Steriade M, McCarley RW. *Brain control of wakefulness and sleep*, 2nd ed. New York: Kluwer Academic/Plenum Publishers; 2005.
7. Luppi PH, Fort P. Neurochemistry of sleep. In: Montagna P, Chokroverty S, editors. *Handbook of clinical neurology*. Elsevier: Amsterdam; 2010 (in press).
8. Lu J, Sherman D, Devor M, Saper CB. A putative flip-flop switch for control of REM sleep. *Nature* 2006; *441* : 589-94.
9. Von Economo C. Die Pathologie des Schlafes. In: Bethe A, Bergmann G, Embden G, editors. *Handbuch der normalen und pathologischen physiologie*. Berlin: Springer; 1926. p. 591.
10. Von Economo C. *Encephalitis Lethargica. Its Sequelae and Treatment*. London: Oxford University Press; 1931.
11. Hess WR. Le sommeil. *C R Soc Biol (Paris)* 1931; *107* : 1333.
12. Nauta WJH. Hypothalamic regulation of sleep in rats. An experimental study. *J Neurophysiol* 1946; *9* : 285.
13. Bremer F. *Cerveau "isolé" et physiologie due sommeil. C R Soc Boil (Paris)* 1935; *118* : 1235-41.
14. Batini C, Magni F, Palestini M, Rossi, GF, Zanchetti A. Neural mechanisms underlying the enduring EEG and behavioral activation in the mid-pontine pretrigeminal peparation. *Arch Ital Biol* 1959; *97* : 1-12.
15. Batini C, Palestini M, Rossi GF, Zanchetti A, Moruzzi G, Magoun HW. Effect of complete pontine transections on the sleep wakefulness rhythm; the midpontine pretrigeminal preparation. *Arch Ital Biol* 1959; *97* : 13-25.
16. Sterman MB, Clemente CD. Forebrain inhibitory mechanisms: sleep patterns induced by basal forebrain stimulation. *Exp Neurol* 1963; *6* : 91.
17. McGinty DJ, Sterman MB. Sleep suppression after basal forebrain lesions in the cat. *Science* 1968; *160* : 1253.
18. Sallanon M, Denoyer M, Kitahama K, Aubert C, Gay N, Jouvet M. Long-lasting insomnia induced by preoptic neuron lesions and its transient reversal by muscimol injection into the posterior hypothalamus in the cat. *Neuroscience* 1989; *32* : 669-83.
19. Dikshit VV. Action of acetylcholine on the "sleep center". *J Physiol* 1934; *83* : 42.
20. McCarley RW. Neurobiology of REM and NREM sleep. *Sleep Med* 2007; *8* : 302-30.
21. Chokroverty S. Physiological changes in sleep. In: Chokroverty S, editor. *Sleep disorders medicine: Basic science, technical considerations and clinical aspects*, 3rd ed. Philadelphia: Elsevier/Butterworth; 2009.
22. Hetzel MR, Clark TJH. Comparison of normal and asthmatic circadian rhythms in peak expiratory flow rate. *Thorax* 1980; *35* : 732.
23. Muller JE, Stone PH, Turi ZG, Rutherford JD, Czeisler CA, Parker C, *et al*. Circadian variation in the frequency of onset of acute myocardial infarction. *N Engl J Med* 1985; *313* : 1315.
24. McWilliams JA. Ventricular fibrillation and sudden death. *BMJ* 1923; *2* : 215.
25. Chokroverty S. Sleep deprivation and sleepiness. In: Chokroverty S, editor. *Sleep disorders medicine: Basic science, technical considerations and clinical aspects*, 3rd ed. Philadelphia: Elsevier/Butterworth; 2009.
26. Walker MP, Stickgold R. Sleep-dependent motor memory plasticity in the human brain. *Neuroscience* 2005; *133* : 911-7.
27. Vertes R, Siegel JM. Time for the sleep community to take a critical look at the purported role of sleep in memory processing. *Sleep* 2005; *28* : 1228-33.
28. Chokroverty S. Approach to the patient with sleep complaints. In: Chokroverty S, editor. *Sleep disorders medicine: Basic science, technical considerations and clinical aspects*, 3rd ed. Philadelphia: Elsevier/Butterworth; 2009.
29. National Commission on Sleep Disorders. *Wake up America*. Washington, DC: US Government Printing Office; 1993.
30. Young TB. Epidemiology of daytime sleepiness: definitions, symptomatology and prevalence. *J Clin Psychiatry* 2004; *65* (Suppl 16): 12-6.
31. *International classification of sleep disorders*, 2nd ed. *Diagnostic and coding manual*. Westchester, Illinois, USA: American Academy of Sleep Medicine; 2005.
32. Guilleminauly C, Zupancic M. Obstructive sleep apnea syndrome. In: Chokroverty S, editor. *Sleep disorders medicine: Basic science, technical considerations and clinical aspects*. Philadelphia: Saunders/Elsevier; 2009. p. 319-39.
33. Sanders MH, Strollo PJ Jr, Atwood CW Jr, Stiller RA, O'Donnell CP. In: Chokroverty S, editor. *Sleep disorders medicine: Basic science, technical considerations and clinical aspects*. Philadelphia: Saunders/Elsevier; 2009. p. 340-60.
34. The International Restless Legs Syndrome Study Group (Arthur S. Walters MD - Group Organizer and Correspondent). Towards a better definition of the restless legs syndrome. *Mov Disord* 1995; *10* : 634-42.
35. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisir J. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep Med* 2003; *4* : 101-19.

36. Xiong L, Turecki G, Levchenko A, Gasper C, Hening WA, Montplaisir J. Genetics of restless legs syndrome. In: Hening WA, Allen RP, Chokroverty S, Earley C, editors. *Restless legs syndrome*. Philadelphia: Saunders/Elsevier; 2009. p. 31-49.

37. Boeve BF, Silber MH, Saper CB, Ferman TJ, Dickson DW, Parisi JE, *et al*. Pathophysiology of REM sleep behavior disorder and relevance to neurodegenerative disease. *Brain* 2007; *130* : 2770-88.

38. Trenkwalder C, Earley CJ. Neuroimaging in restless legs syndrome. In: Hening WA, Allen RP, Chokroverty S, Earley C, editors. *Restless legs syndrome*. Philadelphia: Saunders/ Elsevier; 2009. p. 78-82.

39. Jouvet M, Delorme F. Locus coeruleus et sommeil paradoxal. *C R Soc Biol* 1965; *159* : 895-9.

40. Pevernagie DA, Boon PA, Mariman AN, Verhaeghen DB, Pauweis RA. Vocalization during episodes of prolonged expiration: a parasomnia related to REM sleep. *Sleep Med* 2001; *2* : 19-30.

41. Vertrugno R, Provini F, Plazzi, Vignatelli L, Lugaresi E, Montagna P. Catathrenia (nocturnal groaning): a new type of parasomnia. *Neurology* 2001; *56* : 681-3.

42. Siddiqqi F, Walters AS, Chokroverty S. Catathrenia: a rare parasomnia which may mimic central sleep apnea polysomnogram. *Sleep Med* 2008; *9* : 460-1.

43. Monroy PG, da Fonesca MA. The use of botulinum toxin-a in the treatment of severe bruxism in a patient with autism: a case report. *Spec Care Dentist* 2006; *26* : 37-9.

Reprint requests: Dr S. Chokroverty, Professor of Neuroscience & Co-Chair for the Department of Neuroscience, Program Director, Divisions of Sleep Medicine & Clinical Neurophysiology at the NJ Neuroscience Institute at JFK Medical Center Edison, NJ & Seton Hall University, South Orange, NJ, & Clinical Professor of Neurology at Robert Wood Johnson Medical School, New Brunswick, NJ, USA
e-mail: schok@worldnet.att.net