Sleep Disorders (Dr. Merchut)

1. Stages of sleep

The different stages of sleep are characterized by the cortical activity ("brain waves") recorded by the scalp electrodes of an electroencephalogram (EEG). As sleep begins, the subject progresses "down" through stages 1, 2, 3, and 4 of non-rapid eye movement (NREM) sleep, then reverses "up" stages 3 or 2 before the first rapid eye movement (REM) stage occurs for the night. Stage 1 consists of drowsiness and early EEG slowing. In stage 2, the subject is asleep but easily aroused, and unique sleep spindles appear on the EEG. Sleep deepens in stages 3 and 4, where the subject is harder to arouse, and the slowest (delta wave) EEG activity is recorded.

The first REM period occurs about 90 minutes after sleep begins, and reoccurs about every 90 minutes thereafter, lasting only a few minutes at first, and subsequently lengthening in duration to an hour or so. More time is spent in stages 3 and 4 earlier in sleep, while longer REM periods occur later in sleep. Limb hypotonia is maximal in REM sleep, where subjects are noted to have subtle twitches of the face and limbs, irregular pulse and breathing, and usually horizontal, rapid, conjugate eye movements. In REM, the EEG recording is similar to that of the wake state. Recalling dreams occur in REM and this stage is important for reinforcing memory traces. Deprivation or suppression of REM sleep results in anxiety, hostility, hallucinations and amnesia. Certain drugs, such as the barbiturates, used long ago to induce sleep, are known to suppress REM. Subjects who are deprived of sleep overall will have an earlier onset of REM when allowed to sleep.

Sleep changes with the age of the subject. Newborns sleep about 15 hours daily, consisting of frequent yet shorter sleep periods. Sleep lasts about 6 hours in the elderly, although they have more frequent drowsy periods. The percentage of REM sleep falls from almost 50% in infants to about 20% in older subjects. The percentage of slow wave sleep (stages 3 and 4) decreases, and the percentage of stage 1 and 2 sleep increases with age.

2. The neuroanatomy of sleep

The ascending reticular activating system (ARAS) is important for arousal or wakefulness. It arises from the rostral pons, caudal midbrain, posterior hypothalamus and basal forebrain nuclei to activate the cerebral cortex directly or via the thalamus. The ARAS suppresses the ventrolateral preoptic area of the hypothalamus. A lesion of the ARAS, such as an ischemic infarct of the upper brain stem, produces persistent somnolence or even coma. A pontine "REM center" activates the brain stem gaze centers responsible for the characteristic rapid, conjugate eye movements during REM, and induces hypotonia and increased autonomic activity by descending reticulospinal pathways. REM and NREM sleep are promoted by the preoptic area of the ventrolateral hypothalamus, which receives input from the suprachiasmatic nucleus and has receptors for sleep-inducing peptides and cytokines. Certain cytokines released during systemic infections thus appear responsible for the lethargy experienced with such illnesses. The hypothalamic suprachiasmatic nucleus is the "biological clock"
controlling the circadian sleep-wake cycle. It receives direct retinal input via the adjacent optic chiasm, allowing environmental light stimuli to influence the "clock."

3. Sleep apnea

   Bed partners may be the only observers to note that a subject, often a heavy snorer, periodically ceases breathing while asleep. The patient may feel restless throughout the night, and often feels unrefreshed when waking up in the morning or after a nap. Several serious consequences exist if sleep apnea is not diagnosed and treated. **Daytime sleepiness** may be excessive, to where the patient falls asleep during meals or tasks, and may cause serious motor vehicle accidents. Frequent sleep apneas create nocturnal hypoxemia which in turn can cause pulmonary hypertension or cardiac arrhythmias. **Obstructive sleep apnea** is caused by upper airway obstruction despite contraction of the diaphragm and chest wall muscles. Patients are typically obese, with anatomy predisposing to obstruction, such as short, thick necks or fleshy pharyngeal tissue. The diagnosis is made by an overnight sleep study, including EEG, EKG, oximetry, respiratory and videotape monitoring. Treatment consists of weight loss, surgical correction of the upper airway (uvulopalatopharyngoplasty) or mask devices which deliver pressurized oxygen during sleep. **Central sleep apnea** occurs in the absence of any diaphragmatic or respiratory effort to breathe. It is a rare type of sleep apnea, often without any upper airway obstruction, and of unclear mechanism. Patients with central sleep apnea may need mechanical ventilation while they sleep.

4. Narcolepsy

   Narcolepsy, often an inherited disorder, basically consists of **REM sleep occurring at inappropriate times.** It is related to a deficiency of certain neurons in the dorsolateral hypothalamus which release the excitatory peptide **hypocretin** (also called orexin), and project to the locus ceruleus and cholinergic neurons of the basal forebrain. The classic features include narcoleptic attacks, cataplexy, sleep paralysis and visual hallucinations when falling asleep or waking up. **Narcoleptic attacks** are abrupt, often multiple, intrusions of sleep during daytime activities. **Cataplexy** consists of the periodic loss of muscle tone, for seconds to several minutes in duration, often provoked by emotional triggers, such as an angry outburst, laughing at a joke or being "surprised" by someone. The patient slumps to the ground because of REM limb hypotonia and may not be able to speak well, yet breathes, stays awake and recalls the event. **Sleep paralysis** occurs when REM hypotonia transiently prevents the patient from getting out of bed on wakening. The recallable dreams of REM are the basis for the **vivid hallucinations** experienced by narcolepsy patients when falling asleep (hypnagogic hallucinations) or waking up (hypnopompic hallucinations).

   The diagnosis is confirmed by **multiple sleep latency tests**, where the abnormally **early onset of REM** is recorded as the patient is allowed to fall asleep several times (but not in a state of sleep deprivation). Certain HLA genotypes associated with narcolepsy can be found with blood tests. Narcolepsy poses safety risks for the patient and bystanders, regarding operation of a motor vehicle or machinery. Frequent, planned daytime naps may lessen the sleep attacks. Medications to enhance wakefulness include
amphetamine-like stimulants (methylphenidate) and stimulants unrelated to amphetamine (modafinil, armodafinil). Although its pharmacological mechanism is unclear, modafinil is also helpful in treating the daytime somnolence from sleep apnea. Drugs with REM suppressing properties, such as tricyclic antidepressants, are helpful in reducing cataplexy.

5. Other sleep disorders

**Insomnia** is a common problem, where there is an inadequate quantity and quality of sleep to maintain normal daytime behavior. Various factors impair the initiation or maintenance of sleep, such as jet lag, changing shift work, painful systemic disease, drug addiction or psychiatric illness. Hypnotic medications are helpful for short-term insomnia, but other serious underlying issues need to be addressed in those with chronic insomnia. Disorders of stage 4 sleep include *somnambulism* (sleep walking), sometimes associated with bed-wetting in children, and outgrown with age. **Night terrors** often occur in stage 4 sleep in children. **REM behavior disorder** involves another abnormality of REM sleep, where typically older male patients lack the normal hypotonia of REM. They appear to be "acting out" their dreams, vigorously kicking, punching or running during REM, to the point of injuring themselves or their bedpartner. REM behavior disorder often precedes the onset of Parkinson's disease or Lewy body dementia.