

Lecture series – The Physiology of Sleep
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History

Hippocrates (? c.460 to 377 or 359 BC) born and practiced on the Island of Cos. Described sleep disorders, including insomnia and nocturnal epilepsy. Hippocrates was aware of the dangers of sleep deprivation as well as excessive sleep, and excessive daytime somnolence.

Best description of narcolepsy was by Gélinau, J B in 1880 [Gélinau, J B “De la narcolepsie”, *Gaz Hôp Paris* (1880) 53, 626 - 628, 635 - 627]

Von Economo, a Viennese psychiatrist described the encephalitis lethargica epidemic (1917-1927). One group of patients who slept too much had, at autopsy, lesions in the mesencephalic tegmentum and posterior hypothalamus. A second group, insomniac patients, had lesions mainly in the forebrain. [von Economo, C. *Die Pathologie des Schlafes* In: Bethe A. von Bergman, G A, Embden, G and Ellinger, A. in (eds) *Handbuch der Normalen und pathologischen Physiologie*. Berlin: Springer (1926) Vol 17s 591-610.]

Macnish, P. Macnish suggested there were two forms of sleep, complete sleep with total suppression of movement sensation and all mental activity, and incomplete sleep with retention of some mental activity as in dreaming. However he did not recognise the different stages of sleep. [“The Philosophy of Sleep” Glasgow; E.McPhun (1830).]

Bremer, F: was the first to show striking changes in electrical activity of the brain during sleep. [Bremer, F. *Cerveau isolée et physiologie du sommeil*. C.R. Soc. Biol. (1935) 118. 1245-1241.]

Loomis et al delineated five different patterns of EEG activity connected with different states or levels of sleep. [Loomis A.L.; Harvey, E.N. and Hobart, G.A. “Potential rhythms of the cerebral cortex during sleep”, *Science* (1935) 81, 597-598 and subsequent publications.]

Moruzzi and Magoun had published a paper in 1949 entitled “Brain-stem reticular formation and activation of the EEG”.

Aserinsky and Kiehlman (1955) from Chicago reported during sleep, “periodic rapid eye movements occurred, different from slow, rolling eye movements” (first description of REM sleep). [Aserinsky, E and Kiehlman, N “Regularly occurring periods of eye motility and concomitant phenomena during sleep”, *Science* (1953). 118, 273-274]

Dement and Kleitman. Periodic eye movements (REM sleep) were first recognised to be associated with dreaming. [Dement, W.C. and Kleitman, N “The relation of eye movement during sleep to dream activity. An objective method for the study of dreaming”. *J. Exp. Psychol.* (1957) 53, 339-346.]

Moruzzi and Jouvet (same period) showed that EEG and behavioural changes were dependent on specific neurochemical mechanisms and the activity of brain-stem nuclei and areas extending from the medulla to the posterior diencephalon (1963-1969).

GREEK MYTHOLOGY

Hades (also called Pluto) was the god of the Underworld. Within the Underworld flowed several subterranean rivers: Acheron, the Cocytus, the Phlegethon, the Lethe and the Styx. The Acheron was a main river with its tributaries, the Cocytus, swelled by the Phlegethon. the Lethe and the Styx. To cross Acheron (and hence the Styx) it was necessary to apply to old Charon, the official ferryman of the Underworld. The cost of the journey across the river was an obolus (one-sixth of a drachma, about a penny, so everyone could afford the trip). The Greeks therefore always put an obolus on the tongue of the deceased before burial. Guarding the Underworld was Cerberus, the monster watchdog with fifty heads (sometimes also three heads). He was born of the giant Typhoeus and the goddess Echidna (echidna is one of the few mammals which does not have REM sleep). Those who drank the waters of the Lethe forgot the past, and Lethe flowed to the extremity of the Elysian fields where they would live in peace and harmony, and also to the end of Tartarus, where the bad were punished (i.e. Christian Hell).

Hades had several auxiliaries including Thanatos (Death), who supplied Hades with his subjects. Thanatos was usually represented as a winged spirit and completely resembled his brother Hypnos (Sleep) who lived with him in the Underworld. Hypnos put men to sleep by touching them with his wand, or fanning them with his large wings. The son of Hypnos was Morpheus, God of dreams while Asclepius, the God of Health and Healing and son of Apollo, learned the science of medicine from the centaur, Chiron, but was later killed by Zeus by raising the dead Hippolytus to life. His daughter was Hygieia, and her sister was Panacea. All these deities were worshipped by the Greeks.

What is the physiologic price we pay for sleep?

Definition of sleep: A reversible behavioural state of perceptual disengagement from and unresponsiveness to the environment. A complex amalgam of physiological and behavioural processes.

Although sleep can usually be identified by sustained quiescence in a species-specific posture accompanied by reduced responsiveness to external stimuli, a definition of mammalian sleep requires the additional criteria of:

- (1) quick reversibility to the awake condition;
- (2) characteristic changes in the EEG;
- (3) quick reversibility of sleep is distinguishable from coma and hypothermic states (hibernation).

Sleep is present in mammals and birds (and therefore probably dinosaurs) and is also found in invertebrates (quiescent behaviour). Behavioural quiescence to a stereotypic, species, posture.

Slow-wave sleep has been identified in all birds and mammals studied to date. The absence of REM sleep in the echidna may be due to the echidna's possession of a surprisingly large cortex enabling it to get by without PS.

Stage II. Background of low-voltage mixed frequency with steep spindles (12-14 cps). (> or = 0.5 seconds)

K complex: negative sharp waves followed by a slower, positive component (> or 0.5 seconds). Stage II comprises 45%-55% of sleep.

Stage III: > 20% to < 50% of high amplitude ($> 75\% \mu V$). Slow frequency ($< \text{or} = 2 \text{ cps}$) maximal and frontal. Comprises 3%-8% of sleep.

Stage IV: > 50% high amplitude, slow frequency, comprises 10%-5%.

Non-REM sleep comprises 75%-80% of sleep.

REM sleep is relatively low voltage mixed frequency (like being awake), hence paradoxical sleep. Saw-tooth waves. Theta activity and slow alpha.

REM sleep usually comprises 20%-25% of sleep, carrying four to six discrete episodes. (? discrete). REM sleep associated with phasic rapid eye movements, tonic suppression on EMG with phasic twitches. (atonia/all muscles flaccid except diaphragm and external ocular muscles)

Sleep occurs in approximately 90 to 100 minute cycles throughout the night, starting with Stage I and moving progressively through II, III and IV, followed by REM sleep. Progression from Stages I to IV is associated with increased arousal threshold, ie, it becomes increasingly more difficult to wake a person up.

- Slow-wave sleep is maximal in young children and decreases rapidly with age. A
- Age-related decline in nocturnal slow-wave sleep may parallel loss of cortical synaptic density.
- By age 60 slow-wave sleep may no longer be present particularly in REM (women's libbers would be happy).
- Slow-wave sleep predominates in the first third of the night, and REM sleep in the latter third of the night.

Babies and young children go directly from awake into REM sleep (pathological in adults, usually indicating narcolepsy or severe sleep deprivation).

Shortened REM latency (time taken to get into REM sleep, normally around 90-100 minutes is pathological in adults, ie < 15 minutes is very abnormal).

Other changes on going to sleep:

1. Automatic behaviour: Visual and auditory responses, impaired response to meaningful stimuli abnormal.
2. Hypnic myoclonia (hypnic jerks on going to sleep) sometimes associated with vivid visual imagery.
3. Hypnagogic hallucinations sleep paralysis. Hypnagogic hallucinations, sleep paralysis, excessive daytime somnolence, cataplexy and early-onset REM are all features of narcolepsy.

Sleep is important for consolidation of memory. Waking within 30 seconds of sleep will have less impact on memory consolidated during the ten minutes prior to sleep, than waking ten minutes after sleep onset (the latter causes increases in retrograde amnesia for a longer period prior to sleep onset, eg forgetting a phone call during the middle of the night or not remembering the ringing of your alarm clock).

Stage I sleep is associated with low-arousal threshold. Sign of severely disrupted sleep is an increase in the percentage of Stage I sleep.

Length of sleep: Genetic determinants of length of sleep required from person to person.

Factors modifying sleep stage distribution

Age

Slow wave sleep is maximal in young children and decreases markedly with age. Very young children spend a large proportion of time asleep – a neonate as much as 16 hours/day with approximately 50% of sleep being REM and 50% non-REM. By six months more adult cyclical sleep is becoming consolidated. Premature infants – REM sleep time can be as high as 80% at thirty weeks. Babies and young children show clear distinction between two sleep phases with conspicuous fast and slow eye movements, multiple twitching, facial smiles, grimaces and frowns, lip sucking, small amplitude limb and finger movements, brief vocalisations and transient eye openings during active sleep. All these movements become less obvious with growth and by the age of one, children spend 12 to 13 hours asleep per day, 30% of which is REM sleep and by adolescence, a little over 20% is REM (total sleep time approximately eight hours).

Chronic sleep deprivation causes short microsleeps during wakefulness (short burst of one to ten seconds of Stage 1 sleep with loss of alpha activity, synchronised 4 – 7 Hz activity or onset of Stage 1 non-REM sleep. Observations from de Manacéine (1897) describes:

“Infantry often falls asleep during forced marches: in such cases they continue to make all the necessary movements, walk at a regulated pace, hold their guns etc without awakening”

Prior Sleep History

The total sleep while slow-wave sleep tends to be preferentially recovered versus REM sleep which tends to recover only after the recuperation of slow-wave sleep.

Circadian Rhythm (suprachiasmatic nucleus)

Sleep onset is likeliest to occur on the falling rhythm of the daily temperature cycle (falling in late evening and early afternoon). REM sleep in particular occurs with circadian distribution, but peaks in the morning hours coinciding with the troughs of body temperature. If sleep onset is delayed until the peak REM phase of the circadian rhythm, early morning REM sleep will tend to dominate and may even occur at the onset of sleep.

Temperature

In humans and other species so that mammals have only minimal, if any, ability to thermoregulate during REM sleep (your three year old crawling into your bed before dawn, feeling cold). Shivering during sleep in response to ambient temperature extremes occurs in non-REM sleep and ceases in REM.

Drug Ingestion

Benzodiazapines, eg Temazepam, tend to suppress slow-wave sleep and have no consistent effect on REM sleep. Tricyclic antidepressants, eg Prothiaden and MAO-inhibitors suppress REM sleep. Withdrawal from drugs causes rebound of the sleep stage suppressed.

Alcohol

Pre-sleep alcohol produces REM suppression early in the night followed by REM rebound in the latter night. Warning: Sleep apnoea and alcohol.

Pathology

Narcolepsy

Sleep apnoea syndromes

Fragmentation of sleep due to medical disorders, pain etc.

Circadian phase shifts/shift work/chronic sleep deprivation/jet lag.

Circadian Time-keeping System for Sleep:

- 1845: Davey reports a 24 hour rhythm in his body temperature.
- In 1896 Patrick and Gilbert report first human sleep deprivation experiment and note that body temperature shows a daily cycle during continuous wakefulness.
- In 1923 Kleitman reports intensive study of physiology of sleep loss.
- Aschoff (1954) coins the term Zeitgeber (German for time giver) to describe variations in exogenous factors which influence endogenous rhythms.
- In 1959 Alberg termed the phase “circadian” (about a day) to specify daily endogenous biological periodicities that are often not exactly 24 hours and is influenced by sociological factors. Rest activity variables are the most powerful synchronisers (Zeitgebers) for circadian rhythm in humans.
- Mills in 1964 and 1965, demonstrates a free-running rest-activity rhythm slightly longer than 24 hours in humans living for long periods in temporal isolation.
- In 1968 Rechtschaffen and Kales published a standardised manual for scoring human sleep studies in four stages of non-REM and one stage of REM sleep.

Additional References

Hippocratic Writings. Ed. Lloyd, G E R. Penguin Books 1983.

New Larousse Encyclopaedia of Mythology (1994) Hamlyn Publishing Group. London. Ed. Félix Guirand.

Parkes, J D. Sleep and its disorders (1985) W. B. Saunders Company. London.

Kryger M H, Roth, T, Dement, W C. Principles and Practice of Sleep Medicine (1989) W B Saunders Company, Philadelphia.

Rechtschaffen, A and Kales, A (eds). A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects (1968) Brain Information Service, Brain Research Institute, University of California, Los Angeles, California.