History of Sleep Research From Cave Men to Drosophila

William C. Orr PhD
Lynn Health Science Institute
University of Oklahoma Health Sciences Center
The History of Sleep Research

Phase I prior to 1900-back to Aristotle
Phase II 1900-the discovery of brain waves (1930)
Phase III 1930-1950 emergence from “darkness”
Phase IV 1950-1980 the Gold Rush!!
Phase V 1980-present mining the gold
Start At The Beginning: Where Are We Now?

• In 1996 the AMA recognized sleep medicine as a medical specialty---a very long, arduous journey!!
• Final recognition of the relevance of a phenomenon which has been of interest to man since time began
Aristotle and Ancient Thinkers

• Ancient thinking was largely focused on dreams which reflected the condition of one’s soul rather than physical state
• Aristotle began to think in terms of sleep in more physical terms and separate from dreams
  – He viewed sleep as a loss of sensation and the ability to consume nutrients
  – Nutrient consumption would warm the brain and the ultimate cooling of the brain results in blood rushing to the heart and causing the heart to inhibit it’s sensory function resulting in sleep.
  – All animals must have sleep alternating with wakefullness since the sense organs would be “exhausted” after periods of prolonged waking
Hippocrates and Sleep

• “Sleep is due to blood going from the limbs to the inner regions of the body.“
• “In whatever disease sleep is laborious, it is a deadly symptom.”
• "… I have known many persons in sleep groaning and crying out, some in a state of suffocation, some jumping up and fleeing out of doors, and deprived of their reason until they awaken, and afterward becoming well and rational as before, although they be pale and weak; and this will happen not once but frequently."
Galen (AD 129-199)
Aristotle and Ancient Thinkers

• Galen (AD 129-199) revoked Aristotle’s notion of the heart as the primary organ and focused on the brain

• He noted alterations in sleeping patterns as a sign of disease and as a means of restoring health

• He emphasized the need to keep a proper balance between the amount of time spent sleeping and waking

• Thinking that sleep was a homogenous state, opposed to waking was dominant

• Used valerian root to treat insomnia
The Age of Dreaming--17th and 18th Centuries

• Research on sleep continued it’s focus on the nature and meaning of dreams
• “…dreams offered a diagnostic window into the state of the dreamers soul, rather than his or her body.” Kroker, 2007 (The Sleep of Others)
• Sleep was considered a private function and not the province of systematic scientific research
• 18th century physicians began to abandon the phenomenon of dreams and began to see sleep itself as a means to promote and improve health
19th Century

• 1809 Rolando noted that removal of the cerebral hemispheres in pigeons resulted in a state of permanent sleepiness
• Later Magoon and Moruzzi (1949) showed that the cerebral hemispheres receive arousal signals from the brainstem reticular activating system
19th Century—Sleep and Breathing

• In 1877 W.H. Broadbent a London physician published an article in The Lancet in which he described sleep related breathing problems: “When a person...is lying on his back in heavy sleep and snoring loudly, it very commonly happens that every now and then the inspiration fails to overcome the resistance in the pharynx of which stretor or snoring is the audible sign, and there will be perfect silence through two, three or four respiratory periods, in which there are ineffectual chest movements; finally, air enters with a loud snort, after which there are several compensatory deep inspirations before breathing settles down to its usual rhythm.

• Richard Caton, who discovered the electrical activity of the brain, also presented a patient to the Clinical Society of London in 1888 which he incorrectly diagnosed with narcolepsy, but who we would now recognize as having sleep apnea.
Where Were We Then and Where Are We Now?

- “Sleep is the intermediate state between wakefulness and death; wakefulness being regarded as the active state of all the animal and intellectual functions, and death as that of their total suspension.” The Philosophy of Sleep” Robert McNish 1834

- “In this short period of time (1930-1990 approx.) researchers have discovered that sleep is a dynamic behavior. Not simply the absence of waking, sleep is a special activity of the brain, controlled by elaborate precise mechanisms.” Sleep J. Allen Hobson, 1989

- We have moved into the realm of sleep as an active process of the brain identifying two different and new states of consciousness (REM and NREM)
19th Century – Other Ideas

• Eminent American physiologist William Henry Howell proposed that sleep was the result of diminished blood flow to the brain

• This was an expansion of an idea proposed by Alexander Hammond another American physiologist—ie waking activity demanded greater blood flow to the brain and when activity diminished so did blood flow to the brain and sleep ensued

• This concept failed to adequately account for the inherent cyclic nature of sleep
The Discovery of Narcolepsy

• French neurologist Gelineau first described narcolepsy in 1880
  – First patient was described as having sleep episodes which could occur at anytime; during meals, at the theater, during conversation
  – Distinguished these patients from epileptics—patients could be awakened from “attacks” similar to normal sleep
  – Described cataplexy and dubbed the disease “narcolepsy”

• Proposed a center for emotional associations in the mid brain

• Was not fully accepted as an important and specific sleep disorder until the discovery of REM sleep in the early 1950’s
19th Century—Sleep and Breathing

- Recognition of two control systems for respiration—voluntary during waking and automatic during sleep
- John Cheyne (Irish physician) first described a sleep related breathing disorder in 1818
  - Examined a 60yr. old man with heart disease who breathed ‘strangely’ during sleep
  - “…his breathing was irregular; it would entirely cease for a quarter of a minute, then it would become perceptable, …then by degrees it became heavy and quick, and then it would gradually cease again…”
- In 1854 a similar patient was described by Stokes (also an Irish physician) who attributed the disorder to heart disease
Further Observations On Breathing During Sleep

• Richard Caton (discoverer of the electrical activity of the brain) presented a case to the Clinical Society of London in 1888 which he erroneously diagnosed as narcolepsy
  – “When in sound sleep a very peculiar state of the glottis is observed, a spasmodic closure entirely suspending respiration….The acute dyspnœic attack does not awaken the patient…If in the midst of the dyspnœic attack, he is forcibly aroused, the glottic spasm at once relaxes. The night nurses state that these attacks go on throughout the night.”
  – Christopher Heath, who was the chairman of this session pointed out the similarity between the description of this patient and Joe The Fat Boy from the Dickens novel “The Posthumous Papers of the Pickwick Club” which was published in 1835

• Sir William Osler, noted in his celebrated textbook of medicine the term “Pickwickian Syndrome” to describe obese sleepy patients
Player's Cigarettes.

The Fat Boy. Pickwick Papers.
19th Century

• In 1834 Robert McNish published an influential volume on sleep “The Physiology of Sleep”
  – Supported the notion that sleep was caused by a vascular congestion in the brain
• Sleep had not emerged as a topic of scientific investigation and was largely noted as an experiential phenomenon
• How much sleep one needed was considered purely individualistic and there were no normative data on sleep
• Industrialization, improvements in street lighting and policing rendered the night more like the day and periods of uninterrupted sleep at night became more common
• In this context the term “insomnia” re-emerged – derived from the negation of the Latin word somnus
• Insomnia was seen as the sign of an underlying mental disorder
Henri Pieron (1881-1964)

- French experimental psychologist published “Le Probleme Physiologique Du Sommeil” in 1913
- Characterized sleep physiologically in a modern scientific way
- Framed sleep as a topic as an experimental subject worthy of investigation in its own right
  - Used a method of enforced wakefulness to assess the function of sleep
  - First to investigate sleep in an experimental physiological framework
- Described a “hypnotoxin” extracted from a sleep deprived animal would induce sleep when infused into another animal
- This was later reproduced by Papenheimer and colleagues
Pieron’s PhD Thesis

- Kleitman wrote in 1923 “One of the best books ever written on the subject of sleep”
- Kleitman was a post doctoral fellow under Pieron
- Kroker wrote “His study of sleep was clearly designed to shape as an experimental and theoretical object worthy of investigation in its own right…” (The Sleep of Others)
Brain Wave Activity and Sleep

- Hans Berger described brain wave activity during sleep and waking in 1929 showing clear differences between sleeping and waking
- Sleep could now be studied without disturbing the sleeper
- This represents a major turning point in sleep research allowing an objective and observable description of sleep
- Loomis, Harvey, and Hobart used the EEG to describe different stages of sleep in 1937..stages A-E
Bremer’s Classic Studies

- 1935-1936 studies using the EEG
- Encephale isole—transection at the level of the medulla, isolating the pons from external input
  - Showed oscillation between waking and sleep
- Cerveau isole—transection at the level of the mid pons
  - Showed no oscillation between states of consciousness
- Conclusion: mid brain area controls sleep and waking states
Where Are We Now After Bremer’s Findings (1938)

- Sleep is a recognizable and identifiable state which is distinctly different from waking
- Sleep is a state of the brain which can be identified by the electrical activity of the brain
- Different areas of the brain appear to control different states of consciousness
- It took about 1500 years to get to this point!!
Preparing For The “Gold Rush”

- The description of the reticular activating system by Moruzzi and Magoun in 1949 which when activated produced an arousal pattern in the cortical EEG
- This allowed a correspondence of EEG frequency and behavioral activation
Reticular Activating System
Early Observations On The Mechanisms of Sleep

• Epidemic of encephalitis lethargica from 1916-1930 killed 5 million

• Von Economo conducted autopsies of victims and noted:
  – Those with excessive sleepiness (many died while asleep) had lesions of the posterior hypothalamus
  – Those who experienced total insomnia had lesions of the anterior hypothalamus

• These observations have been confirmed by more recent and sophisticated anatomical observations
The Gold Rush!!

• Nathanial Kleitman (1895-1999)
• Interested in how circadian clocks controlled the sleep wake cycle
• He and a research assistance spent 32 days in Mammoth cave to see if they could adapt to a 28 hour day without any environmental cues----results were inconclusive
• Approximately 30 years Aschoff and Wever studied subjects isolated in an underground WWII bunker
  – They measured body temperature and urine output
  – Established that in the absence of environmental cues the endogenous circadian clock has a periodicity of slightly over 24 hrs (24.2hrs)
Accomplishments of Nathanial Kleitman

• “Sleep and Wakefulness” published in 1939 is the publication that put sleep “on the map” as a legitimate scientific endeavor
• Was interested in ocular movements in infants as a measure of levels of sleep in infants
  – Slow rolling eye movements were present at sleep onset and disappeared as sleep deepened
• Graduate student Eugene Aserkinsky was assigned the laborious task of observing eye movements in sleeping infants
  – He noted an apparent cycle of eye movements in infants
  – They used electro-oculography to investigate this phenomenon in adults
  – During sleep they observed bursts of eye movements which were very different from those observed at sleep onset
The Discovery of REM Sleep

• These observations lead to two assumptions
  – These eye movements represented a “lightening” of the depth of sleep
  – Since they were associated with irregular respiration and accelerated heart rate, they might represent dreaming
  – No continuous EEG was recorded (they only sampled at periodic intervals to conserve paper and money---no grant!)

• They did initiate a small series of awakenings during these different periods of eye movements to elicit dreams

• This lead to the conclusion that the REMs were indeed associated with dreaming

• This publication in Science in 1953 revolutionized the field

• This did not describe REM as a distinct state of consciousness
Wm. C. Dement and REM Sleep

- After the initial publications describing the occurrence of eye movements Aserinsky left Kleitman’s lab
- Dement was an MD/PhD student working in Kleitman’s lab at that time and took over Aserinsky’s role in the sleep lab
- He and Kleitman then became interested in a more in depth description of the eye movement phenomenon
- They began to record the EEG during the entirety of the night and published another landmark study in 1957
  - Described the cyclic occurrence of REM
  - Suggested a REM as a different state of consciousness
- Subsequent studies with animals revealed the unique suppression of spinal motor activity during REM sleep
The Duality of Sleep

• Michel Jouvet and colleagues showed that sleep consists of two fundamentally different states (REM and NREM)

• REM is associated with the suppression of peripheral muscle tone and EEG activation

• Pontine brainstem mechanisms are the primary site for the control of REM sleep
The Discovery of Sleep Apnea

- First clinical discovery of a major sleep disorder since Gileaneau described narcolepsy over 100 years earlier (1880)
- Revolutionized sleep research and catapulted sleep into prominence in the public and in medicine
- First described by two groups at nearly the same time (1965)
  - Gastaut, Tassinari, and Duron in France
  - Jung and Kulo in Germany
- Other early significant contributors were Lugasresi and Coccagna and others in Italy and France described the many clinical consequences of sleep apnea
- Lugasresi also later described snoring as part of the clinical spectrum of sleep apnea
- Early contributors in North America (noted in Lavie’s book “Restless Nights” (all noted in the early 1970s)
  - Lavie at UCSD
  - Orr and Imes at Presbyterian Hospital and OUHSC
  - Meir Kryger at McGill University and University of Manitoba
  - Guilleminault and Dement at Stanford University
Other Milestones in Sleep Apnea Research

• Wisconsin cohort study published by Terry Young and colleagues in NEJM (NEJM 1993; 328: 1230-1235)
  – Noted 25% men and 10% women had an AHI of at least 5
  – When complaints of EDS were taken into account it was determined that 4% of men and 2% of women had OSAS
  – Brought to the fore the issue of sleep apnea as a major public health problem

• Sullivan’s discovery of positive airway pressure as an effective treatment for sleep apnea
  – Revolutionized the treatment of sleep apnea

• This allowed a non-invasive effective treatment of a major sleep disorder

• This, along with PSG as an accurate method to diagnosis allowed sleep to ultimately become a recognized medical specialty
Other Milestones in Sleep Research

• Hobson and McCarley’s model of the neural control of sleep
  – Described the neural feedback systems which controlled the oscillation of REM and NREM sleep
  – Stimulated much work on the neural control of REM sleep

• Rechtschaffen’s work on sleep deprivation
  – Classic studies which helped to describe the need for sleep and it’s vital function
  – What is the function of sleep….focus on these issues was a major contribution

• Mary Carskadon’s work on the sleep of children and adolescents and the discovery of the MSLT
  – Allowed an understanding of the functional importance of sleep as a developmental issue
  – Allowed the objective assessment of daytime sleepiness

• Discovery of the role of the SCN in the regulation of sleeping and waking
The functional effect of circadian regulation is to provide a temporal organization of wake and sleep to permit maximally effective adaptive waking behavior.

Genetics and Sleep

• New frontier of sleep research
• Fruit fly studies have shown genetic differences in long sleepers and short sleepers!!
• Genetic control systems can account for circadian oscillations at the cellular level
• Sleep phenotypes can be created by altering genes in mice and fruit flies
Genetic Control Of The Circadian Clock

- Circadian timing is an inherited adaptation and is therefore genetically determined
  - Fundamental basis of circadian timing comes from the interaction of transcriptional feedback loops
  - Approximately 8% of the brain transcriptome is expressed in a circadian manner
- Critical genes involved in circadian timing:
  - Period (per) gene (Per1, Per2, Per3 all map to a single genetic locus)
  - Cryptochrome (cry) gene
  - Clock gene
  - Bmal 1 gene
- Polymorphism in the Per3 gene has been associated with delayed sleep phase syndrome
- Clock mutant mice show decrease in NREM sleep of 1-2 hrs
The End

• In 1992 The National Commission on Sleep Disorders Research, chaired by William Dement, presented its final report to congress

• Today sleep deprivation and sleep disorders in aggregate remain a pervasive public health problem
If sleep does not serve an absolutely vital function, it is the biggest mistake the evolutionary process ever made.

Alan Rechtschaffen