A Brief History of Sleep and Anesthesia

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Sleep is the basis of our experiential knowledge of unconsciousness and thus often serves as a metaphor for general anesthesia in the clinical setting. In this chapter, we review the history of sleep research, as well as the early development of anesthesiology. A later chapter will discuss the converging neuroscience of sleep and general anesthesia.

Sleep

Although many scientists had investigated whether neural tissue was intrinsically capable of generating electrical signals, research was technically limited in the late 19th and early 20th centuries. It was the discovery and subsequent use of the electroencephalogram (EEG) in 1925 by German scientist Hans Berger[1] that catapulted the investigation of the neural activity during sleep and arousal. Before Berger developed the EEG, 4 scientists found that neural activity in animals produced electrical changes that were detectable by the galvanometer.[2]

Luigi Galvani[3] (1737 to 1798) initiated this line of investigation, proposing that neural tissue was able to produce an electrical impulse when stimulated. Galvani demonstrated that the nerve has conductive abilities enabling it to transmit electrical signals to muscle and therefore generate a contraction.[3] Subsequent research was conducted by

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Johannes Muller and his colleague Emil Du Bois-Reymond.[2] Like Galvani, Du Bois-Reymond[4] used a frog neuromuscular unit and electrically stimulated the peripheral nerve to observe a very brief electrical change, later known to be the compound action potential. English scientist Richard Caton[5] documented voltages of differing frequencies and short amplitudes from the scalps of animal brains; he demonstrated that electrical responses might be generated in select cortical areas as a result of appropriate sensory stimulation. Caton[5] further proposed that cortical rhythms oscillate depending upon states of consciousness—Adolf Beck (1863 to 1942) reached similar conclusions.

Although these 4 scientists concluded that electrical signals exist in the brains of animals, such signals had yet to be validated in humans. In 1924, Hans Berger first performed work on the human brain through the use of electrodes placed on the scalp surface to measure voltage changes. Berger initially used a galvanometer to record the impulses, but in 1925 was the first to actually record electrical signals with an EEG, which indeed showed oscillating electrical activity during sleep and waking.[1] Because of the development of the EEG, scientists were ultimately able to distinguish between rapid eye movement and nonrapid eye movement sleep.

Two other technologic improvements advanced the investigation of sleep: the stereotaxic frame and the cathode ray oscilloscope.[2] The stereotaxic instrument was significant because it allowed targeting and stimulation of subcortical regions of the brain.[6] Victor Horsley (1857 to 1916) and Robert Clarke (1850 to 1926) are credited for the design of the instrument; they based the device on rectilinear coordinates in each of 3 axes.[6] The instrument holds the head rigidly in place and the probe is able to move along the 3 axes to a specific brain region. The 2 scientists subsequently realized that they would require some form of reference of brain structures to match their stereotaxic coordinates; Clarke and his collaborating colleague E. Erskine Henderson are responsible for creating the stereotaxic brain atlas.[7]

The second technologic advance, the cathode ray oscilloscope, allowed researchers to record neural activity from a single nerve cell.[2] With this development, scientists were able to detect such transient voltage changes that occurred from a single cell action potential. The oscilloscope resembles a vacuum tube that has supplementary circuits for voltage amplification and for the direct manipulation of electron streams.[8] Working at Washington University in St. Louis, Joseph Erlanger and Herbert Gasser designed the vacuum tube amplifier to be able to detect low-level electrical signals.[9,10] Erlanger and Gasser pioneered the means to document and subsequently measure "action potentials from peripheral nerves with different diameters and conduction velocities.[2]"

Another significant contribution to sleep research developed at the end of World War I, during which a flu epidemic plagued individuals worldwide. One of the manifestations of the disease, encephalitis lethargica, was noted to induce a persistent vegetative state that routinely proved fatal. Austrian psychiatrist Constantin Von Economo[11,12] (1876 to 1931) analyzed the postmortem brains of those who had suffered the disease and realized that there existed a loss of nerve cells in the posterior hypothalamus, and the mesencephalic reticular formation. Von Economo also studied the brains of patients who displayed chronic insomnia, the converse symptom of the comatose individuals, and discovered a loss of cells in the anterior hypothalamus and the preoptic basal forebrain region.[12] Von Economo's research is the first evidence to suggest that the posterior hypothalamus and the mesencephalic reticular formation were responsible for waking, and the anterior hypothalamus and preoptic area were responsible for sleep.[12]

Further research was conducted about the brain areas affected during sleep by Frederick Bremer (1892 to 1982), who performed 2 surgical operations, known as the encéphalé isolé (separation of brain from body) and the cerveau isolé (separation of anterior midbrain).[13,14] From these procedures, Bremer concluded (1) the spinal cord does not contain the neural mechanisms for sleep and waking and (2) arousal and waking demands some form of sensory stimulation and that sleep is induced and sustained as a result of elimination of sensory input to the telencephalic region of the brain.[13,14] This could be characterized as a passive sleep theory.

In 1948, after the conclusion of World War II, Giuseppe Moruzzi and Horace Magoun studied the inhibitory effects of stimulation of the motor cortex activity of a cat brain; they wanted the brain's EEG to resemble high voltage, low frequency waves that characterize deep sleep, that were able to be desynchronized into the opposite EEG pattern, characteristic of the arousal state. Moruzzi and Magoun[15] were actually stimulating a region of the brain known as the reticular formation, and they discovered that, upon stimulation, the cortical EEG did indeed shift into low voltage, high frequency waves that were not simply localized to the motor cortex, but rather the total cortical surface. As the strength of the applied stimulus amplified, the duration of the arousal response increased. The reticular formation and its surrounding circuits came to be recognized as the ascending reticular activating system (ARAS) and are responsible for the maintenance of consciousness and cortical arousal.[16] After Moruzzi and Magoun's discoveries, the nuclei that were included in the ARAS were revealed as the pedunculopontine tegmental nucleus and the laterodorsal tegmental nucleus, both of which are located in the rostral reticular formation.[17] Both nuclei are characterized by neurons that produce acetylcholine, indicating that this neurotransmitter is critical for arousal states.[18,19]

These cholinergic nuclei were also subsequently shown to be important for REM sleep, which was discovered by Aserinsky and Kleitman in 1953.[20,21]

In the mid-to-late 1950s, after it was accepted that elimination of sensory input induces sleep, work was done by researchers Paul Dell and colleagues[22] that revealed that brain areas are capable of receiving excitatory deactivating signals as well. Dell and colleagues[22] demonstrated that 2 parts of the brain, specifically the cerebral cortex and the lower brain stem, were sending deactivating signals to the ARAS. In the late 1950s, Bonvallet and her colleague Hugelin[23–26] conducted an experiment involving the masseteric stretch reflex, which is mediated by sensory and motor branches of the trigeminal nerve. After administering electrical stimulation to the reticular formation, arousal occurred and a pronounced jaw reflex was noted. When the stimulation remained at a constant level without fluctuations, however, the amplitude of the reflex rapidly disintegrated to the prestimulation levels. Upon removal of the cerebral cortex, the reticular stimulation had the same marked facilitation on the jaw, but the reflex strength did not disintegrate but was preserved as a function of length of reticular stimulation. This revealed that a fully functioning cerebral cortex is somehow able to modulate its degrees of arousal via inhibitory signals to the ARAS.[23–26] In 1961, Dell and colleagues[22] also established that the brainstem is capable of generating both ascending and descending inhibitory signals; this discovery was later confirmed by Maura Mancia, who validated that, upon stimulation, the brain stem indeed sends ascending inhibitory signals that decrease neural activity in the posterior reticular formation as well as in other diencephalic regions associated with arousal.[22]

In 1964, Dahlstrom and Fuxe[27] established the presence of serotonin neurons in a brain region that runs along the midline of the brain stem. It was noted that, upon destruction of this brain structure, chronic insomnia ensued.[27] Others established that serotonin secretion from the raphé nuclei dorsalis was not conducive to sleep.[28,29] In 1944, Rudolph Hess[30] noted that low frequency stimulation of the medial thalamus provoked behavioral sleep in cats. In multiple articles, researchers Morison and Dempsey[31–34] demonstrated that low frequency shocks delivered to the medial, intralaminar, and midline thalamic nuclei generated a distinctive pattern of EEG synchronization known as "recruiting waves" that were observed after stimulation in the cortex of the cat; these recruiting waves resemble sleep spindles, seen in nonrapid eye movement stages 2 and 3. Recruiting waves during slow-wave sleep more accurately correspond to the shape of spontaneous sleep spindles–these waves are in direct opposition to the restricted style of recruiting that is obtained from states of arousal,[35] leading to the belief that, when activated, the aforementioned nuclei of the thalami

trigger a response that produces the EEG pattern characteristic of spindle sleep.

In the 1960s, Barry Sterman and Carmine Clemente[36,37] discovered the importance of the basal forebrain (extending from the rostral basal forebrain to the preoptic area and anterior hypothalamus) in sleep production when they recorded a synchronized EEG pattern after electrically stimulating this area. In 1963, Hernandez-Peon[38] and fellow researchers working in Mexico City demonstrated that the administration of the neurotransmitter acetylcholine could activate the basal forebrain to generate behavioral sleep. Shortly thereafter, another significant brain region associated with sleep was revealed when Clemente[39] and colleague Peñazola-Rojas found that electrical activation of the orbital gyrus (situated ventrally to the frontal cortex) in cats generated a synchronized EEG pattern and behavioral sleep.[40] The view that has been held consistently since the 1970s since Sterman and Clemente's research is that the basal forebrain, specifically the preoptic region and the anterior hypothalamus, are the primary areas to which sleep generation is localized,[36,37] as Von Economo correctly deduced.[12]

■ General Anesthesia

Although the first public demonstration of ether as an anesthetic was performed in 1846, it is possible that the 8th century Arabian philosopher Jabir ibn Hayyam may have been the first to create ether.[41] Raymond Lully, a 13th century European alchemist may also have synthesized ether. Diethyl ether was known in the 16th century to Valerius Cordus and Paracelsus after they observed its anesthetizing effect on chickens, which recovered from the induced sleep unscathed. Nitrous oxide was the other anesthetic commonly used in the mid 19th century and was discovered in 1772 by Joseph Priestley. Nitrous was later investigated in 1800 by chemist Humphrey Davy, who often inhaled the gas himself and noticed that after a brief period of manic euphoria, sleep was induced. He subsequently suggested that nitrous oxide might be useful during a surgical operation.[42]

In the mid 19th century, the battle to claim credit for the discovery of surgical anesthesia was waged by 4 men, each of whom made significant contributions to the beginnings of anesthesiology. On March 30, 1842, Crawford W. Long performed the first surgical procedure using ether as an anesthetic agent.[43] In the 1830s, Long enrolled in medical school at Transylvania University of Kentucky, where the students were taught that ether was an antispasmodic and produced effects that were similar to intoxication, although less potent than alcohol.[44] Long completed his medical training at the University of Pennsylvania, where he often attended "ether frolics" or gatherings where ether was inhaled for its enjoyable effects.[45] His friends often

discussed their recreational use of nitrous oxide for inhalation and Long attempted to convert them to ether inhalation.[43] While under the influence of ether, Long noticed that his friends would habitually run into things that inflicted injury, but they did not appreciate the pain until afterwards.[43] These observations led Long to postulate that ether might be administered during surgery to eliminate pain.[43] James W. Venable was the first patient Long tested: Venable inhaled ether from a towel, before and continuously during a surgery to remove 2 large neck cysts.[43] He later acknowledged that he felt no pain during the surgical procedure. After the successful procedure on Venable, Long chose not to publish his results because he wanted to further use the technique to confirm that it was indeed the ether, rather than the imagination, that produced the anesthesia.[43] By 1846, Long successfully performed 6 to 8 painless operations using ether.[46] Even after his discovery of ether anesthesia, Crawford Long continued to practice medicine and—unlike the other men who contributed to the discovery—did not deeply involve himself in the bitter battle over priority. He regarded ether anesthesia as a means to improve the health of the patient in his direct care.

In 1844, Gardner Colton from Vermont brought medicine to Broadway when he presented an exhibition of men inhaling nitrous oxide. At the beginning of his show, Colton lectured about the history of nitrous oxide and demonstrated how it was created. Among those present in the audience was Horace Wells, who was a practicing dentist in Hartford at the time.[42] During the show, Wells and one of his acquaintances inhaled the nitrous oxide: in the midst of manic hilarity, one acquaintance was injured but felt no pain.[42] Wells speculated that a tooth might be extracted without the sensation of pain under the influence of nitrous oxide. He subsequently opted to have his own tooth extracted, specifically choosing a wisdom tooth to test the efficacy of nitrous oxide as an effective analgesic.[42] The tooth was smoothly and painlessly removed by a Dr John Riggs. Consequently, Wells spread the news to his fellow dentists about the anesthetic utility of nitrous oxide, and many successfully learned how to administer it to their patients.[42]

Wells subsequently made plans to present his discovery in Boston, and arranged a meeting with Dr John C. Warren, a noted surgeon at the Massachusetts General Hospital. In January of 1845, Warren authorized Wells to administer nitrous oxide for another tooth extraction at Harvard Medical School. Unfortunately, Wells had difficulty obtaining quality nitrous oxide in Boston and the demonstration went awry when the patient groaned during the procedure.[42] The students mocked Wells by shouting "Humbug!" and he returned to Hartford dejected. Among those present in the audience, however, was William Thomas Green Morton, a dentist and a former business partner of Wells. After the failed attempt of Wells, Morton sought a more powerful anesthetic agent.

Charles T. Jackson, a graduate of Harvard Medical School and also a passionate geologist and chemist, claimed the discovery of ether anesthesia in 1842. Around this time, Jackson created and developed one of Boston's most advanced laboratories and was recognized throughout the city as a superb analytical chemist. Although it is likely that Jackson did not foresee ether's potential as a surgical anesthetic, he did note that etherization produced a state of insensibility that proved effective for a rather short dental procedure. He never tested his discovery on a surgical patient.[42] Jackson subsequently became a Professor of Chemistry at Harvard Medical School and served as one of William Morton's lecturers while he was in attendance there. Thus, Morton first learned about the chemistry of ether from Jackson, when in 1844 he provided a demonstration to his class that the inhalation of sulfuric ether was conducive to loss of consciousness.[42]

Morton began experimenting with inhaled ether. Liquid ether could be transported in bottles and could be easily inhaled due to its volatility.[41] Liquid ether also possessed rather unique characteristics that offered latitude to a relatively unskilled administrator: at levels of surgical anesthesia, there existed minimal hypoventilation and uptake was slow, which minimized the potential for overdosage. After testing ether on numerous animals, Morton reportedly performed etherization on his dental patients. In 1846, he obtained an invitation by John C. Warren to publicly administer ether to patient Edward Gilbert Abbott at the Massachusetts General Hospital in the Bulfinch amphitheater.[41] On October 16, 1846, a tumor on the jaw was to be removed by Dr Warren with Morton administering the anesthetic. The procedure was in fact postponed because Morton had to wait for an engineer, Wightman, to produce a temporary inhaler.[41]

After the surgery, Abbott reported that, although he was cognizant of the surgery, he felt no pain.[47] Abbott's report established etherization as one of America's greatest contributions in the 19th century. Warren recognized the significance of the event at the time of the operation, turning to his students and proclaiming, "Gentlemen, this is no humbug." Morton wished to safeguard his name on the ether patent and refused to reveal the ingredient of the compound he named "Letheon.[41]" He subsequently revealed the primary ingredient as ether, and although news of Morton's successful demonstration of a painless surgical operation spread around the world, it was still many years before surgical anesthesia was accepted and recommended.[41]

James Young Simpson, a Scottish obstetrician, was the first to use ether to minimize pain during labor.[41] Simpson found the slow uptake and onset of ether analgesia to be disadvantageous and sought out a faster-acting agent, testing chloroform in 1847.[41] Although the use of anesthesia during labor was at first controversial, as many believed it was in opposition to God's will, it eventually secured acceptance when

physician John Snow administered it to Queen Victoria during her deliveries. She was allowed to inhale chloroform through a handkerchief and was delighted with the relief of pain—the monarch's approval of chloroform quelled all debate on the matter.[41]

In 1848, John Snow introduced an inhaler after he concluded that a successful anesthetic agent must not only eliminate pain but also suppress movement.[41] With use of an animal model, he established the concentration that would be needed to preclude movement in response to noxious stimulation.[41] Snow's work presaged the modern idea of minimum alveolar concentration and he also acknowledged the connection between solubility, vapor pressure, and anesthetic potency, all of which were not fully recognized until after the conclusion of World War II.[41]

The first half of the 19th century gave rise to the first generation of inhaled anesthetics: ether, nitrous oxide, and chloroform.[41] In the second half of the century and the early 20th century, inhaled anesthetics such as ethyl chloride, ethylene, and propylene were also employed. Ethyl chloride was typically used as a topical anesthetic, as the compound's rapid evaporation temporarily froze skin when the agent was sprayed on it.[41] The rediscovery of the compound was made in 1894 by a Swedish dentist named Carlson who sprayed the ethyl chloride into a patient's mouth to freeze an abscess and the patient subsequently lost consciousness.[41] Ethylene gas had been used to prevent the opening of carnation buds in greenhouses and in 1923 speculation arose that the gas could have an anesthetic effect on humans. The enthusiasm was quelled when it was discovered that it took rather large concentrations of the pungent, explosive agent to anesthetize a human.[41]

In 1929, an accidental experiment led to the discovery of propylene as a possible anesthetic agent.[48] When fresh, propylene demonstrated effective anesthetic properties, but when stored, the chemical degraded into a compound called cyclopropane that produced nausea and cardiac arrhythmias in humans.[41] Chemist George Lucas combined a low concentration of cyclopropane with oxygen and administered the mixture to 2 kittens who were temporarily anesthetized and awoke unharmed.[41] Lucas concluded that cyclopropane was a powerful anesthetic, which proved to be stable after storage.[48] Research and experimentation were thwarted after anesthesia-related deaths occurred in Toronto, but were later resumed by Dr Ralph Waters, who successfully tested the drug at the University of Wisconsin.[49] Concurrently, Chauncey Leake and MeiYu Chen performed successful laboratory demonstrations of divinyl ether, or vinethene, in 1930. It was not until later in the 19th century that fluorinated anesthetic agents were introduced and approved.[41]

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