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History of Sleep Medicine

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Sleeping and dreaming always have been a fundamental part of human existence. Most early writing on these subjects almost entirely was speculation. During the twentieth century, however, scientific observation and experimentation abounded. This article emphasizes the evolution of the key concepts and research findings that characterize sleep research and sleep medicine, crucial discoveries and developments in the formative years of the field, and those principles and practices that have stood the test of time. Early writings are reviewed by others [1].

Sleep as a passive state

Sleep is the intermediate state between wakefulness and death; wakefulness is regarded as the active state of all the animal and intellectual functions and death as that of their total suspension [2].

The foregoing thought is how Robert MacNish, a member of the faculty of physicians and surgeons of Glasgow starts his book, *The Philosophy of Sleep,* published in 1834. This sentence highlights the major watershed in the history of sleep research and sleep medicine—early notions of sleep as a passive process gave way to notions of sleep as an active process. Until the discovery of rapid eye movements (REMs), sleep was regarded universally as an inactive state of the brain, which occurred as the inevitable result of reduced sensory input. Waking up and being awake were considered a reversal of this process, occurring mainly as a result of bombardment of the brain by stimulation from the environment. No clear distinction was seen between sleep and other inactive states, such as coma, stupor, intoxication, hypnosis, anesthesia, and hibernation.

In addition to the reduction of stimulation, a host of less popular assumptions was proposed to account for the onset of sleep, including vascular theories and various versions of a "hypnotoxin" theory, in which

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fatigue products, toxins, and so forth were accumulated during the day, finally causing sleep, during which they were eliminated gradually [3]. It has been observed since biblical times that alcohol and other compounds, such as opium, induce a sleep-like state and that coffee and caffeine have the power to prevent sleep.

In the 1920s, the University of Chicago physiologist, Nathaniel Kleitman, embarked on his lifelong career as a sleep researcher. He performed a series of sleep deprivation studies and made the simple but brilliant observation that individuals who stayed up all night generally were less impaired and sleepy the next morning than in the middle of their sleepless night. Kleitman argued that this observation was incompatible with the notion of a continual buildup of a hypnotoxin in the brain or blood. In addition, he believed that human beings were approximately as impaired as they could get, that is, very impaired, after approximately 60 hours of wakefulness and that longer periods of sleep deprivation produced little additional change. In the 1939 (first) edition of his landmark monograph, *Sleep and Wakefulness*, Kleitman [4] wrote,

> It is perhaps not sleep that needs to be explained, but wakefulness, and indeed, there may be different kinds of wakefulness at different stages of phylogenetic and ontogenetic development. In spite of opinions that sleep is an actively initiated process, by excitation or inhibition or cortical or subcortical structures, there is not a single fact about sleep that cannot be equally well interpreted as a let down of the waking activity.

The electrical activity of the brain

In 1875, the Scottish physiologis Richard Caton demonstrated electrical rhythms in the brains of animals. It was not until German psychiatrist Hans Berger [5] recorded electrical activity of the human brain, however, beginning in 1928, and demonstrated clear differences in these rhythms when subjects were awake or asleep that a real scientific interest commenced. Berger inferred correctly that the signals he recorded, which he called electroencephalograms, were of brain origin. For the first time, the presence of sleep could be established conclusively without disturbing the sleeper, and, equally important, sleep could be measured continuously and quantitatively without disturbing the sleeper.

Davis and Harvey and their coworkers [6–8] at Harvard University described all the major elements of sleeping brain wave patterns in an important series of articles published in 1937, 1938, and 1939. Blake and colleagues [9,10] at the University of Chicago extended those observations. In the human electroencephalogram (EEG), sleep is characterized by high-amplitude slow waves and spindles, whereas wakefulness is characterized by low-amplitude waves and alpha rhythm. The image of the sleeping brain as completely turned off gave way to the image of the sleeping brain as engaged in slow, synchronized, idling neuronal activity.

The 1930s also saw one series of investigations that seemed to establish conclusively that sleep occurred passively in response to reduction of stimulation and activity. These investigations were performed by Frederic Bremer and reported in 1935 and 1936 [11,12]. Bremer studied brain wave patterns in two cat preparations. One, which Bremer called encéphale isolé, was made by a transection in the lower part of the medulla oblongata. The other, cerveau isolé, was made by transecting the midbrain just behind the origin of the oculomotor nerves. The first preparation permitted the study of cortical electrical rhythms under the influence of olfactory, visual, auditory, vestibular, and musculocutaneous impulses; in the second preparation, the sensory input was narrowed almost entirely to the influence of olfactory and visual impulses.

In the encéphale isolé preparation, the brain continued to present manifestations of wakeful activity alternating with phases of sleep as indicated by the EEG. In the cerveau isolé preparation, however, the EEG assumed a definite deep sleep character and remained in this condition. In addition, the eyeballs immediately turned downward and the pupils became miotic. Bremer concluded that sleep is associated with a functional (reversible) deafferentiation of the cerebral cortex. The cerveau insolé preparation results in a suppression of the incessant influx of nerve impulses, particularly cutaneous and proprioceptive, which are essential for the maintenance of the waking state of the telencephalon. Bremer concluded that olfactory and visual impulses are insufficient to keep the cortex awake.

The ascending reticular system

After World War II, insulated, implantable electrodes were developed, and sleep research in animals began in earnest. In 1949, one of the most important and influential studies dealing with sleep and wakefulness was published. This was Moruzzi and Magoun's classic article, "Brain Stem Reticular Formation and Activation of the EEG." These investigators [13] concluded that

> … transitions from sleep to wakefulness or from the less extreme states of relaxation and drowsiness to alertness and attention are all characterized by an apparent breaking up of the synchronization of discharge of the elements of the cerebral cortex, and alternation marked in the EEG by the replacements of high voltage, slow waves with low voltage fast activity.

High-frequency electrical stimulation through electrodes implanted in the brainstem reticular formation produces EEG activation and behavioral arousal. Thus, EEG activation, wakefulness, and consciousness are at one end of the continuum; sleep, EEG synchronization, and lack of consciousness are at the other end. This view is hardly different from the statement by MacNish quoted at the beginning of this article.

The demonstration by Starzl and colleagues [14] that sensory collaterals discharge into the reticular formation suggests that a mechanism is present

by which sensory stimulation can be transduced into prolonged activation of the brain and sustained wakefulness. By attributing an amplifying and maintaining role to the brainstem core and the conceptual ascending reticular activating system, it was possible to account for the fact that wakefulness can be maintained in the absence of sensory stimulation.

Chronic lesions in the brainstem reticular formation produce immobility and persisting slow waves in the EEG. The usual animal for this research was the cat because excellent stereotaxic coordinates became available [15]. The theory of the reticular activating system was an anatomically based, passive theory of sleep or active theory of wakefulness. The published proceedings of a 1954 symposium, entitled *Brain Mechanisms and Consciousness* [16] (which probably was the first genuine neuroscience bestseller), contains the full flowering of the ascending reticular activating system theory.

Early observations of sleep pathology

Two early observations stand out with regard to sleep research and sleep medicine. The first is the description in 1880 of narcolepsy by Jean Baptiste Edouard Gélineau (1859–1906), who derived the name, narcolepsy, from the Greek words, narkosis (a benumbing) and lepsis (to overtake). He was the first to publish a clear description of the constellation of components that constitute the syndrome, although in 1916 Richard Henneberg coined the term, cataplexy, for the emotionally induced muscle weakness.

The second observation of what might be called the leading sleep disorder of the twentieth century, obstructive sleep apnea (OSA), was made in 1836, not by a clinician but by the novelist Charles Dickens. Dickens published a series, entitled the "Posthumous Papers of the Pickwick Club," in which he described Joe, a loud snorer who was obese and somnolent. The lad also was called Young Dropsy, suggesting he may have had right-sided heart failure. Kryger [17] and Lavie [18] have published scholarly accounts of many early references to snoring and conditions that were most certainly manifestations of sleep apnea syndrome.

Sigmund Freud and the interpretation of dreams

By far the most widespread, although indirect, interest in sleep by health professionals was engendered by the theories of Sigmund Freud. The interest really was in dreaming, with sleep as the necessary concomitant. Freud developed psychoanalysis and the technique of dream interpretation as part of his therapeutic approach to emotional and mental problems. As the ascending reticular activating system concept dominated behavioral neurophysiology, so the psychoanalytic theories about dreams dominated the psychologic side of the coin. Dreams were believed guardians of sleep and to occur in response to a disturbance to avoid waking up, as exemplified in the classic alarm clock dream. Freud's concept that dreaming discharged

instinctual energy led directly to the notion of dreaming as a safety valve of the mind. At the time of the discovery of REMs during sleep (in approximately 1952), academic psychiatry was dominated by psychoanalysts, and medical students all over America were interpreting one another's dreams.

From the vantage point of today's world, the dream deprivation studies of the early 1960s, which were engendered and reified by the belief in psychoanalysis, may be regarded by some as a digression from the mainstream of sleep medicine. Alternatively, because the medical-psychiatric establishment had begun to take dreams seriously, it also was ready to support sleep research fairly generously under the guise of dream research.

Chronobiology

Most sleep specialists share the opinion that chronobiology, or the study of biologic rhythms, is a legitimate part of sleep research and sleep medicine. The 24-hour rhythms in the activities of plants and animals have been recognized for centuries. These biologic 24-hour rhythms were reasonably assumed to be a direct consequence of the 24-hour environmental fluctuation of light and darkness. In 1729, however, de Mairan described a heliotrope plant that opened its leaves during the day, even after de Mairan had moved the plant so that sunlight could not reach it. The plant opened its leaves during the day and folded them for the entire night, even though the environment constantly was dark. This first demonstration of circadian rhythms in the absence of environmental time cues is described in the book by Moore-Ede and colleagues, entitled *The Clocks That Time Us* [19].

Factors that appeared to foster a separate development of chronobiology and sleep research in earlier years were

1. The long-term studies commonly used in biologic rhythm research precluded continuous recording of brain wave activity, which was too difficult and not necessary. Thus, the measurement of wheel-running activity was a convenient and widely used method for demonstrating circadian rhythmicity.
2. The favorite animal of sleep research from the 1930s through the 1970s was the cat, and neither cats nor dogs demonstrate readily defined circadian activity rhythms. The separation was maintained further by the tendency for chronobiologists to know little about sleep and for sleep researchers to remain uninformed about such biologic clock mysteries as phase response curves, entrainment, and internal desynchronization.

The discovery of rapid eye movement sleep

The identification of the discrete organismic state known as REM sleep should be distinguished from the discovery that REMs occur during sleep.

The historical threads of the discovery of REMs are as follows: University of Chicago professor, Nathaniel Kleitman, had long been interested in cycles of activity and inactivity in infants and in the possibility that this cycle ensures that infants have a regular, recurring opportunity to respond to their own increasing hunger. He postulated that the times infants awakened to nurse on a self-demand schedule are integral multiples of this basic rest-activity cycle. Kleitman also was interested in eye mobility as a possible measure of "depth" of sleep. The reasoning for this was that eye movements have a much greater neocortical representation than any other observable motor activity. In addition, slow, rolling, or pendular eye movements were described at the onset of sleep and as gradually slowing and disappearing as sleep "deepened" [20]. In 1951, Kleitman assigned the task of observing eye movement to his graduate student, Eugene Aserinsky. Watching the closed eyes of sleeping infants was tedious, and Aserinsky found that it was easier to designate successive 5-minute epochs as "periods of motility" if he observed any movement (including a writhing or twitching of the eyelids) and "periods of no motility" when he observed no movement.

After describing an apparent rhythm in "eye motility," Kleitman and Aserinsky decided to look for a similar phenomenon in adults. Again, watching the eyes of infants during the day was tedious and at night even worse. Casting about, they came upon the technique of electro-oculography (EOG) and decided, correctly, that it was a good way of measuring eye motility continuously and relieving human observers of the tedium of direct observations. Sometime in the course of recording the EOG during sleep, bursts of electrical potential changes were seen that were different from the slow movements at sleep onset.

When they were observing infants, Aserinsky and Kleitman did not differentiate slow and rapid movements. With the EOG, however, the different nature of the slow eye movements at sleep onset and the newly observed bursts of EOG potentials became obvious. Initially, there was concern that these potentials might be electrical artifacts. With their presence in the EOG as signal, however, it was possible to watch subjects' eyes simultaneously, and when this was done, the distinct rapid movements of the eyes beneath the closed lids were easy to see.

The basic sleep cycle was not identified at this time, primarily because the EOG and other physiologic measures, notably the EEG, were not recorded continuously but were sampled only a few minutes of each hour or half hour. The sampling strategy was used to conserve paper (there was no research grant). Also, at the time, there was not a clear reason to record continuously, and sampling made it possible for investigators to nap between sampling episodes.

Aserinsky and Kleitman initiated a small series of awakenings for the purpose of eliciting dream recall either when REMs were present or when REMs were not present. They did not apply sophisticated methods of dream content analysis, but the descriptions of dream content from the two

conditions generally were different, which made it possible too conclude that REMs were associated with dreaming. This was, indeed, a breakthrough in sleep research [21,22].

The occurrence of the eye movements was compatible with contemporary theories that dreams occurred when sleep lightened to prevent or delay awakening. In other words, dreaming still could be regarded as the "guardian" of sleep. It no longer could be assumed, however, that dreams were fleeting and evanescent.

All-night sleep recordings and the basic sleep cycle

The seminal Aserinsky and Kleitman article was published in 1953. To understand how little attention it attracted, it should be noted that no publications on the subject appeared from any other laboratory until 1959. In the early 1950s, most previous research on sleep physiology either had generalized a single short period of sleep to all sleep or had relied on intermittent sampling during the night. There was no motivation to obtain continuous records during typical nights of sleep.

To describe and quantify the occurrence of REM periods during the night better, however, Kleitman and I [23] performed continuous recording for a total of 126 nights from 33 subjects and, by means of a simplified categorization of EEG patterns, scored the paper recordings in their entirety. When they examined the data from 126 records, they found that there was a predictable sequence of patterns over the course of the night, which had been overlooked entirely in all previous EEG studies of sleep. This sequence of regular variations since has been observed tens of thousands of times in hundreds of laboratories, and the original description essentially has remained unchanged.

The usual sequence was that after the onset of sleep, the EEG progressed fairly rapidly to stage 4, which persisted for varying amounts of time, generally approximately 30 minutes, and then a lightening took place. Although the progression from wakefulness to stage 4 at the beginning of the cycle almost was invariable through a continuum of change, the lightening usually was abrupt and coincident with a body movement or series of body movements. After the termination of stage 4, there generally was a period of stage 2 or stage 3, which gave way to stage 1 and REMs. When the first eye movement period ended, the EEG progressed through a continuum of change to stage 3 or 4, which persisted for a time and then lightened, often abruptly, with body movement to stage 2, which again gave way to stage 1 and the second REM [23].

Kleitman and I found that this cyclical variation of EEG patterns occurred repeatedly throughout the night at intervals of 90 to 100 minutes from the end of one eye movement period to the next. The regular occurrence of REM periods and dreaming strongly suggested that dreams did not occur in response to chance disturbances of sleep.

At the time of these observations, sleep still was considered to be a single state. Kleitman and I characterized the EEG during the REM periods as "emergent stage 1" as opposed to "descending stage 1" at the onset of sleep. The percentage of the total sleep time occupied by REM sleep was between 20% and 25%, and the periods of REM sleep tended to be shorter in the early cycles of the night. This general picture of all-night sleep has been seen over and over in normal human beings of both genders, in widely different environments and cultures, and, for all intents and purposes, across the life span.

Rapid eye movement sleep in animals

The developing knowledge of the nature of sleep with REMs was in direct opposition to the ascending reticular activating system theory and constituted a paradigmatic crisis. The following observations were crucial:

- Arousal threshold in human beings was much higher during periods of REM with a low-amplitude, relatively fast (stage 1) EEG pattern than during similar "light sleep" at the onset of sleep.
- REMs during sleep were discovered in cats; the concomitant brain wave patterns (low-amplitude, fast) were completely indistinguishable from patterns associated with active wakefulness.
- By discarding the sampling approach and recording continuously, a basic 90-minute cycle of sleep without REMs alternating with sleep containing REMs was discovered. The all-night patterns had regular, lawful, predictable patterns of occurrence. Continuous recordings consistently revealed active EEG patterns during the entire period of sleep within which bursts of REM occurred.
- Observations of motor activity in human beings and animals during REM periods revealed the unique occurrence of an active suppression of spinal motor activity.

Thus, it was clear that sleep consists not of one state but rather of two distinct organismic states as different from one another as each is from wakefulness. It had to be conceded once and for all that sleep was not simply a time of brain inactivity and EEG slowing. By 1960, this fundamental advance in thinking about the nature of sleep was well established; it exists as a fact that has not changed in any way since that time.

The discovery of REMs during sleep in human beings plus the all-night sleep recordings that revealed the regular recurrence of lengthy periods during which REMs occurred and during which the brain wave patterns resembled light sleep prepared the way for the discovery of REM sleep in cats. This was in spite of the extremely powerful bias that an "activated" EEG could not be associated with sleep. In the first study of cats, the problems of maintaining the insulation of implanted electrodes was not yet

solved, so an alternative, small pins in the scalp, was used. With this approach, the waking EEG was obscured totally by the electromyogram from the large temporal muscles of the cat. When the cat fell asleep, however, slow waves could be seen, and the transition to REM sleep was observed clearly because muscle potentials were suppressed completely. The cat's REMs and the twitching of the whiskers and paws could be observed directly.

The following note from a more personal account [24] is included to illustrate the power and the danger of scientific dogma.

> It is very difficult today (circa 1990) to understand and appreciate the exceedingly controversial nature of these findings. I wrote them up, but the paper was nearly impossible to publish because it was completely contradictory to the dominant neurophysiological theory of the time. The assertion by me that an activated EEG could be associated with unambiguous sleep was considered to be absurd. As it turned out, previous investigators had observed an activated EEG during sleep in cats [25,26], but simply could not believe it and ascribed it to arousing influences that interrupted the animals' sleep. A colleague who was assisting me was sufficiently skeptical that he preferred that I publish the scientific report as sole author. After four or five rejections, to my everlasting gratitude Editor-in-Chief Herbert Jasper accepted the paper without revision for publication in *Electroencephalography and Clinical Neurophysiology* [27].
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> It is notable, however, that the significance of the absence of muscle potentials during the REM periods in the cats was not fully appreciated. It remained for Michel Jouvet, working in Lyon, France, to insist on the importance on the electromyographic suppression in his early papers [28,29]. Hodes and Dement began to study the "H-Reflex" in human subjects in 1960 and found complete suppression of reflexes during REM sleep [30]. Following this, Octavio Pompeiano and others in Pisa, Italy, worked out the basic mechanisms of REM atonia in the cat [31].

The duality of sleep

Even though the basic non-REM (NREM)-REM sleep cycle was well established, the realization that REM sleep qualitatively was different from the remainder of sleep took several years to evolve. Jouvet [32] and his colleagues performed an elegant series of investigations on the brainstem mechanisms of sleep that forced the inescapable conclusion that sleep consists of two fundamentally different organismic states. Among Jouvet's many early contributions were clarification of the role of pontine brainstem systems as the primary anatomic site for REM sleep mechanisms and the clear demonstration that electromyographic activity and muscle tonus are suppressed completely during REM periods and only during REM periods.

It is an established fact that muscle atonia is a fundamental characteristic of REM sleep and that it is mediated by an active and highly specialized neuronal system. The pioneering microelectrode studies of Evarts [33] in

cats and monkeys and observations on cerebral blood flow in the cat by Reivich and Kety [34] provide convincing evidence that the brain during REM sleep is active. Certain areas of the brain appear to be even more active during REM sleep than during wakefulness. The notion of sleep as a passive process was demolished totally, although for many years there was a lingering attitude that NREM sleep essentially was a state of brain inactivity. By 1960, it was possible to define REM sleep as a completely separate organismic state characterized by cerebral activation, active motor inhibition, and, of course, in humans, an association with dreaming. The fundamental duality of sleep was an established fact.

Premonitions of sleep medicine

Sleep research, which emphasized all-night sleep recordings, burgeoned in the 1960s and was the legitimate precursor of sleep medicine and, in particular, its core clinical test, polysomnography. Much of the research at this time emphasized studies of dreaming and REM sleep and had its roots in a psychoanalytic approach to mental illness. After sufficient numbers of all-night sleep recordings of human volunteers had been performed to document the highly characteristic normal sleep architecture, investigators noted a significantly shortened REM latency in association with endogenous depression [35]. This phenomenon has been investigated intensively ever since. Other important precursors of sleep medicine were:

1. Discovery of sleep-onset REM periods (SOREMPs) in patients who had narcolepsy.
2. Interest, primarily in France, in sleep, epilepsy, and abnormal movement.
3. Introduction of benzodiazepines and the use of sleep laboratory studies in evaluating hypnotic efficacy.

Sleep-onset rapid eye movement periods and cataplexy

In 1959, a patient who had narcolepsy came to see Dr. Charles Fisher, who worked at the Mount Sinai Hospital in New York City. Fisher suggested that a sleep recording might be of interest. Within seconds after he fell asleep, the patient was showing dramatic, characteristic REMs and sawtooth waves in the EEG. The first article documenting SOREMPs in a single patient was published in 1960 by Vogel [36]. In a collaborative study between the University of Chicago and the Mount Sinai Hospital, nine patients were studied, and the consistent occurrence of SOREMPs was described in a 1963 article [37]. Subsequent research showed that sleepy patients who did not have cataplexy did not have SOREMPs, and those who had cataplexy always had SOREMPs [38]. Cataplectic attacks were the normal motor inhibitory mechanisms of REM sleep occurring abnormally.

The narcolepsy clinic: a false start

In January 1963, I was eager to continue studying the association between cataplexy and SOREMPs. Not a single narcoleptic patient could be identified, however. Finally, by placing a brief advertisement in the *San Francisco Chronicle*, more than 100 people responded. More than half of the respondents were bona fide narcoleptics who had sleepiness and cataplexy.

The surprising response to the advertisement was a noteworthy event in the development of sleep disorders medicine. With one or two exceptions, none of the narcoleptics ever had been diagnosed correctly. A responsibility for their clinical management had to be assumed as part of their use in research. The late Dr. Stephen Mitchell, who had completed his neurology training and was entering a psychiatry residency at Stanford University, joined me in 1964 to create a narcolepsy clinic. Soon, we were involved in the medical management of more than 100 patients. Mostly, this entailed seeing the patients at regular intervals and adjusting their medication. Nonetheless, the seeds of the modern sleep disorders clinic were sowed because at least one daytime polygraphic sleep recording was done in each patient to look for the presence of SOREMPs, and patients were questioned exhaustively about their sleep. If possible, an all-night sleep recording was performed. Unfortunately, most of the patients were unable to pay their bills, and insurance companies declared that the recordings of narcoleptic patients were experimental. Because it was unable to generate sufficient income, the clinic was discontinued and the patients were referred back to local physicians with instructions about treatment.

Benzodiazepines and hypnotic efficacy studies

Benzodiazepines were introduced in 1960 with the marketing of chlordiazepoxide. This compound offered a significant advance in terms of safety over the use of barbiturates for the purpose of tranquilizing and sedating. It was quickly followed by diazepam and the first benzodiazepine introduced specifically as a hypnotic, flurazepam. Although questionnaire studies had been done on the effects of drugs on sleep, the first use of the sleep laboratory to evaluate the effect of sleeping pills was the 1965 study by Oswald and Priest [39]. An important series of studies establishing the role of the sleep laboratory in the evaluation of hypnotic efficacy was performed by Kales and colleagues at the University of California, Los Angeles [40]. The group also performed studies of patients who had hypothyroidism, asthma, Parkinson's disease, and somnambulism [41–44].

The discovery of sleep apnea

Possibly the most important advance in the history of sleep disorders medicine occurred in Europe. Sleep apnea was discovered simultaneously by two independent groups, Gastaut and colleagues in France [45] and Jung

and Kuhlo in Germany [46]. Both groups reported their findings in 1965. These important findings were ignored completely in the United States. What should have been an almost inevitable discovery by either the otolaryngologic surgery community or pulmonary medicine community did not occur because there was no tradition in either specialty for observing breathing carefully during sleep. The well-known and frequently cited study of Burwell and coworkers [47], although impressive in a literary sense in evoking the image of Dickens' somnolent fat boy, Joe, erred badly in evaluating their somnolent obese patients only during waking and attributing the cause of the somnolence to hypercapnea.

The popularity of this article essentially eliminated the possibility that the American pulmonary community would discover sleep apnea. To this day, there is no evidence that hypercapnea causes true hypersomnolence, although high levels of P_{CO_2} are associated with impaired cerebral function. Nevertheless, the term, pickwickian, became an instant success as a neologism. This popularity may have stimulated the interest in studying pickwickian patients' syndrome by the aforementioned European neurologists.

A small group of Italian neurologists who specialized in clinical neurophysiology and electroencephalography were in the vanguard of clinical sleep research. One of the collaborators in the French discovery of sleep apnea, Carlo Tassinari, joined Italian neurologist Elio Lugaresi in 1970. These clinical investigators, along with Coccagna and a host of others over the years, performed crucial series of clinical sleep investigations that provided a complete description of the sleep apnea syndrome, including the first observations of the occurrence of OSA in nonobese patients, an account of the cardiovascular correlates, and a clear identification of the importance of snoring and hypersomnolence as diagnostic indicators. These studies are recounted in Lugaresi and colleagues' book, *Hypersomnia with Periodic Apneas* [48].

Italian symposia

In 1967, Gastaut and Lugaresi organized an important meeting (proceedings published as *The Abnormalities of Sleep in Man* [49]), which encompassed issues across the full range of abnormal sleep in humans. This meeting took place in Bologna, Italy, and the presentations covered many of today's major topics in the sleep medicine field: insomnia, sleep apnea, narcolepsy, and periodic leg movements during sleep. It was an epic meeting from the point of view of the clinical investigation of sleep; the only major issues not represented were clear concepts of clinical practice models and clear visions of the high population prevalence of sleep disorders. The meeting that surely triggered a serious international interest in sleep apnea syndromes, however, was organized by Lugaresi in 1972 and took place in Rimini, a small resort on the Adriatic coast [50].

The evolution of sleep medicine clinical practice

The practice of sleep medicine evolved in many centers in the 1970s. The development often was a function of the original research interests of the center. The launching of the world's first sleep disorders clinic in 1970 at Stanford University is described in this article as a harbinger of how sleep medicine subsequently evolved throughout the world.

The use of patients complaining of insomnia in hypnotic efficacy studies brought the Stanford group closely into relation with many insomnia patients and demolished the notion that the majority of such patients were psychiatric subjects. One early question was, "How reliable are the descriptions of their sleep by these patients?" The classic all-night sleep recording could yield a great deal of information. A second factor was that throughout the second half of the 1960s, the research activities of the Stanford group continued to require managing patients who had narcolepsy. As the Stanford clinic's reputation for expertise in narcolepsy grew, it found itself receiving referrals for evaluation from physicians all over the United States. Although the identification of sleep apnea as a frequent cause of severe daytime sleepiness had not yet occurred, several patients referred who had the presumptive diagnosis of narcolepsy did not possess narcolepsy's two cardinal signs, SOREMPs and cataplexy. True pickwickians were an infrequent referral at this time.

In January 1972, Christian Guilleminault, a French neurologist and psychiatrist, joined the Stanford group. He had extensive knowledge of the European studies on sleep apnea. Until his arrival, the Stanford group had not used respiratory and cardiac sensors routinely in their all-night clinical sleep studies. Starting in 1972, these measurements became a routine part of the all-night diagnostic test. In 1974, Gerry Holland, a member of the Stanford group, named the all-night test, polysomnography. Publicity about narcolepsy and excessive sleepiness resulted in a flow of referrals of sleepy patients who had the presumptive diagnosis of narcolepsy to the Stanford sleep clinic. During the first year, the goal of the practice was to see at least five to ten new patients per week. To foster financial viability, the group did as much as possible, within ethical limits, to publicize its services. Accordingly, there also was a sprinkling of patient referrals, often self-referred, who had chronic insomnia. The diagnosis of OSA in patients who had profound excessive daytime sleepiness nearly always was completely unambiguous.

During 1972, the search for sleep abnormalities in patients who had sleep-related complaints continued; the intent was to conceptualize the pathophysiologic process as an entity and as the cause of the presenting symptom. With this approach, several phenomena seen during sleep rapidly were linked to the fundamental sleep-related presenting complaints. Toward the end of 1972, the basic concepts and procedures of sleep disorders medicine were established well enough such that it was possible to offer a daylong course through Stanford University's Division of Postgraduate

Medicine. The course was entitled, "The Diagnosis and Treatment of Sleep Disorders." The topics covered were normal sleep architecture; the diagnosis and treatment of insomnia with descriptions of drug-dependent insomnia, pseudoinsomnia, central sleep apnea, and periodic leg movements as diagnostic entities; and the diagnosis and treatment of excessive daytime sleepiness or hypersomnia, with narcolepsy, NREM narcolepsy, and OSA as diagnostic entities.

The disability and cardiovascular complications of severe sleep apnea were alarming. The treatment options at that time, however, were limited to weight loss and chronic tracheostomy. The dramatic results of chronic tracheostomy in ameliorating the symptoms and complications of OSA had been reported by Lugaresi and colleageus [51] in 1970. The notion of using chronic tracheostomy, however, was resisted strongly by the medical community. The first patient who was referred for investigation of his severe somnolence and eventually treated with tracheostomy was a 10-year-old boy. The challenges that were met to secure the proper management of this patient are worthy of a detailed account (Christian Guilleminault, personal communication, 1990).

Case history

Raymond M. was a 10½-year-old boy referred to the Pediatrics Clinic in 1971 for evaluation of unexplained hypertension, which had developed progressively over the preceding 6 months. There was a positive family history of high blood pressure, but never so early in life. Raymond was hospitalized and had determination of renin, angiotensin, and aldosterone; renal function studies, including contrast radiographs; and extensive cardiac evaluation. All results had been normal except that his blood pressure oscillated between 140-170/90-100. It was noticed that he was somnolent during the daytime and Dr. S. suggested that I see him for this "unrelated" symptom.

I reviewed Raymond's history with his mother. Raymond had been abnormally sleepy "all his life." However, during the past 2 to 3 years, his schoolteachers were complaining that he would fall asleep in class and was at times a "behavioral problem"—not paying attention, hyperactive, aggressive. His mother confirmed that he had been a very loud snorer since he was very young, at least since the age of 2 years, perhaps before.

Physical examination revealed an obese boy with a short neck and a very narrow airway. I recommended a sleep evaluation, which was accepted. An esophageal balloon and measurement of end tidal CO_2 was added to the usual array. His esophageal pressure reached 80 to 120 cm H_2O. He had values of 6% end tidal CO_2 at end of apnea, apneic events lasted between 25 and 65 seconds, and the apnea index was 55. His Sao_2 was frequently below 60%.

I called the pediatric resident and informed him that the sleep problem was serious. I also suggested that the sleep problem might be the cause of the alarming and unexplained hypertension. The resident could not make

> sense of my information and passed it on to the attending physician. I was finally asked to present my findings at the pediatric case conference, which was led by Dr. S. I came with the recordings, showed the results, and explained why I believed that there was a relationship between the hypertension and the sleep problem. There were a lot of questions. They simply could not believe it. I was asked what treatment I would recommend and I suggested a tracheostomy. I was asked how many patients had this treatment in the United States, and how many children had ever been treated with tracheostomy. When I had to answer "zero" to both questions, the audience was somewhat shocked. It was decided that such an approach was doubtful at best, and completely unacceptable in a child. However, they did concede that if no improvement was achieved by medical management, Raymond would be reinvestigated including sleep studies.
>
> This was spring 1972. In the fall he was, if anything, worse in spite of vigorous medical treatment. At the end of 1972, Raymond finally had his tracheostomy. His blood pressure went down to 90/60 within 10 days, and he was no longer sleepy. During the 5 years we were able to follow Raymond he remained normotensive and alert, but I had to fight continuously to prevent outside doctors from closing his tracheostomy. I don't know what happened to him since.

In addition to medical skepticism, a major obstacle in the practice of sleep disorders medicine was the retroactive denial of payment by insurance companies. A 3-year period of educational efforts directed toward third-party carriers by the Stanford group finally culminated in the recognition of polysomnography as a reimbursable diagnostic test in 1975. Another issue was obtaining specific state licensure of an outpatient clinic that offered overnight testing to avoid the licensing requirements of a hospital. This, too, finally was accomplished in 1975.

Clinical significance of excessive daytime sleepiness

Guilleminault, in a series of studies, recognized excessive daytime sleepiness as one of the major presenting complaints and as a pathologic phenomenon unto itself [52]. It was recognized, however, that methods to quantify excessive daytime sleepiness in terms of improvement with treatment were not adequate. The 7-point Stanford Sleepiness Scale developed by Hoddes and colleagues [53] was a first attempt at quantification but did not give reliable results. The problem was not a crisis because patients who had severe apnea and overwhelming daytime sleepiness were improved dramatically by tracheostomy, and the reduction in daytime sleepiness was completely unambiguous. Nevertheless, documenting the objective improvement of sleepiness with pharmacologic treatment of narcolepsy and with tracheostomy in less severe sleep apnea patients continued to be a problem.

An early attempt to develop an objective measure of sleepiness was that of Yoss and coworkers [54]. They observed pupil diameter directly by video

monitoring and described changes associated with sleep deprivation and narcolepsy. Subsequently designated pupillometry, this cumbersome technique has not been accepted widely.

Mary Carskadon deserves most of the credit for the development of the latter-day standard approach to the quantification of sleepiness, the Multiple Sleep Latency Test (MSLT). She noted that subjective ratings of sleepiness made before a sleep recording predicted sleep latency not infrequently. In spring 1976, she undertook to establish sleep latency as an objective measurement of the state of sleepiness alertness by measuring sleep tendency every 2 hours before, during, and after 2 days of total sleep deprivation [55]. The choices of a 20-minute duration of a single test and a 2-hour interval between tests essentially were arbitrary and dictated by the practical demands of that study. The protocol designed for this study has stood the test of time and remains the standard protocol for the MSLT. This new test formally was applied to the evaluation of sleepiness in patients who had narcolepsy [56] and later in patients who had OSA [57].

Carskadon and colleagues then undertook a monumental study of sleepiness by following children longitudinally across the second decade of life, which also is the decade of highest risk for the development of narcolepsy. Using the new MSLT measure, she found that 10-year-old children were completely alert in the daytime. By the time they reached sexual maturity, however, they were no longer fully alert with the same amount of sleep they had obtained when they were 10 years of age. Results of this remarkable decade of work and other studies are summarized in an important review [58].

The important conceptual advances that early MSLT research established were:

1. Daytime sleepiness and nighttime sleep are an interactive continuum, and the adequacy of nighttime sleep absolutely cannot be understood without a complementary measurement of the level of daytime sleepiness.
2. Excessive sleepiness, also known as impaired alertness, arguably is sleep medicine's most important symptom.

Recent history

As the decade of the 1970s drew to a close, the consolidation and formalization of the practice of sleep disorders medicine largely was completed. The Association of Sleep Disorders Centers (now the American Academy of Sleep Medicine) was founded and provided a home for professionals interested in sleep and particularly those who had begun to diagnose and treat sleep disorders. The Association was started in 1975 with five member centers. It was responsible for the launching of the scientific

journal, *Sleep,* in 1978, and it fostered the setting of standards through center accreditation and an examination for practitioners, by which they were designated Accredited Clinical Polysomnographers.

The first international symposium on narcolepsy took place in the French Languedoc in summer 1975 immediately after the Second International Congress of the Association for the Psychophysiological Study of Sleep in Edinburgh. The former meeting, in addition to being scientifically productive, had landmark significance because it produced the first consensus definition of a specific sleep disorder, drafted, revised, and unanimously endorsed by 65 narcoleptologists of international reputation [59]. The first sleep disorders patient volunteer organization, the American Narcolepsy Association, also was formed in 1975. The *ASDC/APSS Diagnostic Classification of Sleep and Arousal Disorders* was published in fall 1979 after 3 years of extraordinary effort by a small group of dedicated individuals who composed the nosology committee, chaired by Roffwarg [60].

Before the 1980s, the only effective treatment for severe OSA was chronic tracheostomy. This highly effective but personally undesirable approach was replaced in 1981 by two new procedures—one surgical [61], the other mechanical [62]. The surgical approach was uvulopalatopharyngoplasty, which is giving way to more complex and effective approaches. The second was the now widely used and highly effective continuous positive nasal airway pressure technique, introduced by Australian pulmonologist Colin Sullivan. The combination of the high prevalence of OSA and the availability of effective treatments fueled a rapid increase in the number of centers and physicians practicing the diagnosis and treatment of sleep disorders. The decade of the 1980s was capped by the publication of the field's first textbook, *Principles and Practice of Sleep Medicine* [63].

The decade of the 1990s saw acceleration in the acceptance of sleep medicine throughout the world [64]. In the United States, the National Center on Sleep Disorders Research (NCSDR) was established by statute as part of the National Heart, Lung, and Blood Institute of the National Institutes of Health [65,66]. The mandate of NCSDR is to support research, promote educational activities, and coordinate sleep-related activities throughout various branches of the government. This initiative led to the development of large research projects dealing with various aspects of sleep disorders and the establishment of awards to develop educational materials at all levels of training.

The 1990s also saw the establishment of the National Sleep Foundation [67] (NSF) and other organizations for patients [68]. The NSF points out to society at large the dangers of sleepiness, and this effort is highlighted during the NSF's annual National Sleep Awareness Week. As the internet increases in size exponentially, so do its sleep resources for physicians, patients, and the public at large [69]. There currently are many Web sites devoted to sleep and its disorders.

The challenge of the future

The greatest challenge for the future is the cost-effective expansion of sleep medicine so that its benefits will be available readily throughout society. A major problem is the current failure of sleep research and sleep medicine to penetrate the mainstream educational system effectively at any level. As a consequence, the majority of human beings remain unaware of important facts of sleep and wakefulness, the fundamentals of biologic rhythms, and knowledge about sleep disorders, in particular the symptoms that suggest a serious pathologic process. The management of sleep deprivation and its serious consequences in the workplace, particularly in those industries that maintain sustained operations, is only beginning to be addressed comprehensively.

Finally, the education and training of health professionals to be sleep specialists has far to go to reach adequate numbers. Sleep medicine is fully established as a clinical scientific discipline, however. It has made a concern for the health of human beings a 24-hour enterprise and has energized a new effort to reveal the secrets of the healthy and unhealthy sleeping brain.

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