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The Development of Sleep Medicine: A Historical Sketch

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For centuries the scope of sleep disorders in medical writings was limited to those disturbances which were either perceived by the sleeper him- or herself as troublesome, such as insomnia, or which were recognized by an observer as strange behavioral acts during sleep, such as sleepwalking or sleep terrors. Awareness of other sleep disorders, which are caused by malfunction of a physiological system during sleep, such as sleep-related respiratory disorders, were widely unknown or ignored before sleep monitoring techniques became available, mainly in the second half of the 20th century. Finally, circadian sleep-wake disorders were recognized as a group of disturbances by its own only when chronobiology and sleep research began to interact extensively in the last two decades of the 20th century. Sleep medicine as a medical specialty with its own diagnostic procedures and therapeutic strategies could be established only when key findings in neurophysiology and basic sleep research allowed a breakthrough in the understanding of the sleeping brain, mainly since the second half of the last century.

Keywords: history, insomnia, hypersomnia, narcolepsy, parasomnia, sleep-related movement disorder, pediatric sleep disorder, sleep apnea, circadian rhythm sleep-wake disorder

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INTRODUCTION

For centuries, knowledge on sleep and its disturbances was based exclusively on self-experience and observation of the behavior of sleeping persons. It was only since the middle of the 19th century that sleep became an object of experimentation, when Kohlschütter (1863) studied the depth of sleep by applying systematically varied acoustic stimuli.[1] In the following decades physiological processes during sleep, such as the distribution of blood volume,[2] muscular fatigue,[3] and the 24-hour rest-activity cycle[4] were investigated. This had become feasible by major advances in natural sciences and instrumentation, which allowed to measure bodily functions of sleeping persons by techniques such as plethysmography[2] and actography.[4] However, since the brain is the essential organ for the regulation of sleep, systematic investigations of sleep had to wait for techniques that enabled the study of brain activity during sleep. Such a method became available with the invention of the electroencephalogram (EEG) by Hans Berger[5] in the second decade of the last century. Only a few years later, advanced technology made it possible to perform continuous registrations of the EEG during sleep in human[6] and animal subjects.[7] In the following years neurophysiological studies with lesion, stimulation, and electrophysiological recording techniques investigated the role of brain stem and midbrain structures for the regulation of sleep, wakefulness, and arousal.[8–10] A turning point in the conception of sleep was achieved finally when rapid eye movement (REM) sleep was detected as a unique state of sleep,[11,12] which differs from NREM sleep not only by its morphology but also by its systemic regulation.[13–15] In combination with an increasing knowledge on sleep physiology, this became the basis for the experimental study of sleep and its disorders in the following decades.[16–18] Results from these research efforts, together with growing clinical experience, mainly from specialized sleep laboratories which were installed in clinical units, led to the conception of a new diagnostic system of sleep and arousal disorders.[19,20] It was also the time when large epidemiological studies on sleep disturbances were first performed,[21,22] while smaller-scale studies on the amount of sleep and sleeplessness in specific groups had already been performed in the first half of the century.[23] Thus, sleep medicine, which is a quite new medical field with a long clinical tradition, developed rapidly in the last three decades of the 20th century.

In the following, historical trends in the clinical description and pathophysiological understanding of the main categories of sleep-wake disorders will be delineated. Some of the currently classified sleep disorders, such as insomnia or nightmare, were described in early Greek, Roman, and Arabic medical treatises (Hippocrates, Dioscorides, Oribasius, Galen, Al Razi, and others), while others were recognized only much later. The documentation of the duration and quality of sleep in patients with any medical disorder and the effect of treatment on sleep always has been part of medical records, as innumerable published patient histories illustrate. Growing knowledge in anatomy, physiology, and pathology led to increasingly refined classification systems of medical disorders, including those of sleep and wakefulness, in the late 18th and early 19th century.[24–26]

INSOMNIA

Insomnia or *agrypnia* is the most common sleep disorder, already mentioned by early medical writers. Although negative

consequences of insufficient sleep on health have been unanimously emphasized, the diagnostic concept of insomnia fluctuated always between insomnia as a symptom or a disorder by itself. Boissier de Sauvages, in his *Nosologia methodica morborum*, cited from the medical literature not less than eleven different diseases, all causing insomnia.[24] The varying nosological concept of insomnia is reflected even today in the three successive editions of the actual classification of sleep disorders.[27] Causes of insomnia are manifold. Beside other diseases and cephalgia, Boissier[24] listed reduced forces (*vires imminuuntur*), restlessness (*inquietudo*), and anxiety, which all may result in increased sensitivity, similar to what is called hyperarousal today.[28] Concerning the pathophysiology of insomnia, in the middle of the 19th century, Durham[29] and Hammond[30] concluded from experiments in animals and from observations in infants and patients that sleep is caused by diminished circulation of blood in the brain. Based on this assumption, Hammond suggested as treatment of pathological wakefulness all those measures which "sooth" the nervous system, reduce the activity of the heart and vessels, and thus reduce the amount of blood in the brain. With the same intention he used potassium bromide as a pharmacological sleep aid, a substance which was assumed to exert an anemic action on the brain and to reduce its reactivity to stimuli.[31] Further progress in the pharmacological treatment of insomnia was made in the second half of the 19th century when new substances with sedating properties, such as chloral hydrate, were synthesized.[32] However, at all times, opinions were divided on the appropriate treatment of sleeplessness. Should medications be given or should other means be installed to reduce the burden of the patient? A strong argument for non-pharmacological treatment was made by James Russell (1861)[33]:

> In treating these cases (of sleeplessness), the key to success lies in the management of the patient's mind, and unless we recognize the large share which is taken by mental disorder in producing and perpetuating the various and puzzling symptoms which present themselves, we shall not only fail in our object, but shall be in danger of actually aggravating the malady. Much may be done by soporifics and tonics; but our chief attention must be directed to regulating and strengthening the mind, otherwise our medicines will only serve to fix the patient's attention more closely upon the symptoms, and induce reliance upon external measures rather than upon self-discipline. The treatment required is suggested by the nature of the malady. We find self-control diminished, the will inert, the emotions dominant, the thoughts of the sufferers occupied entirely about themselves, and the idea of disease the one subject engrossing their attention; we find every sensation registered, every fresh complaint welcomed and symptoms which at first seem to belong to organic disease are discovered, by further experience of the case, to have their origin in nothing but exaggerated sensitiveness or disordered fancy….The task of ministering to such a condition is no light one; and it is hard to say whether the discipline is more severe to the patient or to the attendant. (p. 489)

A new era of pharmacological treatment of insomnia began with the synthetization of the first compound of a new class of hypnotics, the barbiturates, at the beginning of the 20th century.[34] Barbiturates became the leading class of hypnotics until the middle of the 20th century.[35] Beginning in the 1960s, barbiturate hypnotics were replaced by the newly developed benzodiazepines, starting with chlordiazepoxide in 1960 and diazepam in 1963. Next to their sedative potency, the low toxicity of benzodiazepines favored their rapidly increasing role in the treatment of insomnia. In addition, benzodiazepines were the first generation of hypnotics whose efficacy has been tested with the techniques of the newly established sleep laboratories.[36,37] Neuropharmacologic studies showed that benzodiazepines interact mainly with the neurotransmitter γ-aminobutyric acid (GABA) at the $GABA_A$ receptor site. Hypnotic drugs which bind to subsets of the GABA receptor were developed later—today frequently summarized as z-drugs (zopiclone, zolpidem, and zaleplon). A most recent treatment approach is based on the principle to modulate the neurotransmitter orexin or hypocretin that is essentially involved in the regulation of wakefulness.[38]

Although pharmacological substances have been shown to be effective for the treatment of insomnia, problems such as non-responding to treatment, loss of efficacy, unwanted effects such as, e.g., hangover and rebound after discontinuation remain. Thus it is not surprising that the debate how to best treat sleeplessness is ongoing, also in this journal.[39,40] The two main alternatives to drug treatment, namely sleep hygiene and especially "talking medicine" have been developed as competing alternatives since the middle of the last century, mainly using principles of the rapidly growing field of behavioral and cognitive therapy, developed in psychology.[41] Methods which are used in behavior therapy of sleep disorders include sleep restriction,[42] cognitive therapies, rules for sleep hygiene, or a combination thereof,[43] called cognitive behavior therapy (CBT). Comparative studies have suggested similar efficiency of pharmacological and behavioral/cognitive therapies, with the additional advantage of outlasting effects of non-pharmacological treatment after ending of the active intervention.[44]

HYPERSOMNIAS

In contrast to sleeplessness, which is a well-known experience to most people, at least in its sporadic form, pathological sleepiness is not. Impressive, however mostly strange case reports on pathological sleepiness, also called *somnolentia* or *lethargus*, appeared from time to time in the medical literature.[45] Many of these case reports were summed up by Heinrich Bruno Schindler, who added an own extensive case report. The book, which was published in 1829,[46] is probably the first which deals exclusively of hypersomnolence. The author noticed a great variety in the pattern of sleepiness (sleepiness in short intervals, periodic sleep episodes, continuous sleepiness) and its duration (days, months, even years), combined with a characteristic inability to awaken the person from pathological sleep. However, in most of the twenty case reports, the condition remained obscure since the pathophysiological knowledge

was too limited to recognize and to differentiate between neurological, psychiatric, or newly recognized infectious disease causes of prolonged or recurrent states of hypersomnolence. In the 19th and early 20th century, the medical community became aware of three distinct illnesses which all had pathological sleepiness as a prominent symptom.

African Sleeping Sickness

The first event, with an impact on the perception of excessive sleepiness was the confrontation of the colonial authorities with the sleeping sickness or *trypanosomiasis*, an epidemic illness which afflicted African populations. An English physician and abolitionist, Thomas Masterman Winterbottom, who had practiced for four years in Sierra Leone, found sleeping sickness among the inhabitants of Benin. Some years later, when he practiced again in England, he gave an impressive account of the fatal course of the illness.[47]

> The Africans are very subject to a species of lethargy, which they are much afraid of, as it proves fatal in every instance…Children are very rarely, or never, affected with this complaint, nor is it more common among slaves than among free people, though it is asserted that the slaves from Benin are very subject to it. At the commencement of the disease, the patient has commonly a ravenous appetite, eating twice the quantity of food he was accustomed to take when in health, and becoming very fat. When the disease has continued some time, the appetite declines, and the patient gradually wastes away. Squinting occurs sometimes, though very seldom, in this disease, and in some rare instances the patient is carried off in convulsions. Small glandular tumors are sometimes observed in the neck a little before the commencement of this complaint, though probably depending rather upon accidental circumstances than upon the disease itself. Slave traders, however, appear to consider these tumors as a symptom indicating a disposition to lethargy, and they either never buy such slaves, or get quit of them as soon as they observe any such appearances. The disposition to sleep is so strong, as scarcely to leave a sufficient respite for the taking of food; even the repeated application of a whip, a remedy which has been frequently used, is hardly sufficient to keep the poor wretch awake. The repeated application of blisters and of setons has been employed by European surgeons without avail, as the disease, under every mode of treatment, usually proves fatal within three or four months. (p. 29)

Narcolepsy

Second, late in the 19th century, interest in excessive sleepiness was renewed by two case reports on patients who fell asleep repeatedly in inadequate situations and, additionally, experienced sudden drops of muscle tone, typically evoked by surprise or laughter.[48–50] Gélineau (1880) called the disease narcolepsy, derived from the greek *νάρχωσις* (somnolent) and *λαμβάνειν* (seized). Perhaps the disorder had been described already earlier; however, indications of cataplexy were never mentioned.[51] Later observations and research led to the concept of a typical tetrad of symptoms, namely daytime sleepiness, cataplexies, sleep paralysis, and hypnagogic hallucinations.[52] Although a rare disease, neurologists and clinical sleep researchers showed a high interest in narcolepsy since the illness seemed to offer a unique access for the understanding of sleep mechanisms. However, this proved true only much later, when premature occurrence of REM sleep, a state which is characterized by muscle atonia, was found to be a hallmark patients with narcolepsy.[53] Some years later, the known increased risk for the disease in relatives led to the finding that pathomechanisms which may induce narcolepsy are closely linked to the immune system.[54] Finally, molecular genetic studies in animal models of the disease led to the detection of orexin/hypocretin, a transmitter of hypothalamic origin with essential functions for vigilance regulation, which is unusually low or absent in the majority of patients with narcolepsy-cataplexy.[38]

Encephalitis Lethargica

A third event which contributed much to the understanding of sleep regulation and the pathology of excessive sleepiness was the epidemic occurrence of a new infection disease in Europe from 1916 to 1927, called encephalitis lethargica by Constantin von Economo who contributed most to decipher the pathophysiology of this brain disease.[55,56] Most important in the present context was the observation that disorders of sleep were remarkable and regularly occurring symptoms of the disease, either in the form of hypersomnia, agrypnia, or sleep inversion. Based on the study of brain lesions of encephalitis lethargica patients, von Economo suggested the existence of brain stem centers which actively control wakefulness and sleep. He localized these centers at the transition from the mesencephalon to the diencephalon. While lesions of the anterior area (basal forebrain) produced wakefulness, those of the posterior area produced sleep. The inverse was true for stimulation of these areas. The assumption of sleep as an active process, controlled by a subcortical sleep center, was supported by studies of Hess, who showed that sleep could be elicited by stimulation with low frequency electrical current in widely distributed diencephalic areas of freely moving animals.[9] However, at that time the concept of a subcortical sleep center stood in clear contrast to Pavlov's understanding of sleep as a primarily cortical process which was initiated and sustained by cortical inhibition and thus by inhibiting conditioned reflexes which are established during wakefulness.[57] Knowledge on the interplay between cortical and subcortical structures for the regulation of sleep and wakefulness was essentially extended in the late 40s when Moruzzi and Magoun recognized the key role of the brainstem reticular formation (ascending reticular activating system, ARAS) for the regulation of wakefulness and sleep.[10]

Recurrent Hypersomnia

Reports on persons with recurrent attacks of protracted sleep of unclear origin were published occasionally in the medical literature before and during the 19th century.[58,59] Two early Russian case reports by Anfimoff (1898) and Kabanich (1923), which are hardly available, were reproduced in some detail by Kaplinsky and Schulmann.[60] The complex clinical picture of recurrent hypersomnia was further clarified in the early 20th

century by Willi Kleine[61] and Max Levin.[62] Both reported on cases of periodic sleepiness, mostly in young males, which could be associated with episodes of hyperphagia, sexual disinhibition, and other signs of abnormal behavior, which were atypical for the subject when healthy. The term Kleine-Levin syndrome for this rare but impressive form of recurrent hypersomnia was first used by Critchley and Hoffman.[63] These authors suggested a pathophysiological process of unclear nature, affecting the hypothalamus, being responsible for the clinical picture. At present, brain imaging methods are used to better understand the disease process. The method allows to compare brain metabolism in the same patient during symptomatic and asymptomatic episodes.[64]

PARASOMNIAS

Parasomnias represent a heterogeneous group of "undesirable physical events or experiences that occur during entry into sleep, within sleep, or during arousal from sleep…Parasomnias encompass abnormal sleep related complex movements, behaviors, emotions, perceptions, dreams, and autonomic nervous system activity."[27] The term parasomnia was probably first used in 1905 by the Swiss psychologist Edouard Claparède[65] when he differentiated between three forms of pathological sleep, (insomnia, hypersomnia, and parasomnia), and a few years later by Albert Salmon,[66] who summarized nightmares, sleep talking, and sleepwalking as parasomnias. Although the term parasomnia is quite new, many of the sleep disturbances, which belong to this diagnostic category, are known since ancient times.

Sleepwalking

Somnambulism or sleepwalking is the prototype of an observable alteration of normal sleep which aroused interest of philosophers, physicians and layman since ever.[67,68] The 19th century was a peak time of publications on sleepwalking with more papers on this topic than before or after.[69] One reason for that was probably a widespread interest in animal magnetism and "magnetic sleep," i.e., a sleep-like state, frequently associated with a somnambulistic episode, which was induced by magnetizers or hypnotists. As a consequence, many papers of that epoch indicated in the title already whether they dealt with "natural" or "artificial" somnambulism. Early in the 20th century Sadger, a Viennese psychiatrist and disciple of Freud, published a monograph on *Sleep Walking and Moon Walking* wherein he analyzed episodes of sleepwalking of his own patients and from novels. In the frame of psychoanalytic thinking he concluded that sleepwalking represents a motor outbreak of the unconscious and serves, like the dream, the fulfillment of secret, forbidden wishes, mostly of a sexual erotic nature.[70] Later, electroencephalographic studies[71] showed that somnambulistic episodes begin during slow wave sleep, and the EEG during somnambulistic incidents is low voltage with mixed frequencies. If alpha waves occurred, they were not blocked by eye opening. "During the incidents, the sleepwalkers appeared to be aware of their environment but indifferent to it. Their eyes were open, expressions blank, and movements somewhat rigid."[71] The EEG studies confirmed earlier observations of somnambulistic incidents, which occurred preferentially early in sleep, and they helped to solve many questions which had puzzled observers in the past, e.g., whether persons can "see" when they are in a somnambulistic state with eyes open.

Incubus—Nightmare Disorders

A nightly attack by *ephialte* (Greek), *incubus* (Latin), *cauchemar* (French) or *Alp* (German) is such an unusual and horrifying experience that descriptions and conjectures about its origin can be found in medical texts and folklore at all times and in all cultures. A thorough analysis of *incubus* in medieval theology and medicine can be found in Van der Lugt.[72] Paulus Aegineta,[73] a presumably 7th century surgeon of the island of Aegina, gave a concise description[73]:

> Persons suffering an attack experience incapability of motion, a torpid sensation in their sleep, a sense of suffocation, and oppression, as if from one pressing them down, with inability to cry out, or they utter inarticulate sounds. Some imagine often that they even hear the person who is going to press them down, that he offers lustful violence to them, but flies when they attempt to grasp him with their fingers. (p. 388)

However, the concept of nightmare changed quite substantially with time. The idea that the perceived oppression was caused by an outside force or person (*incubus*, *succubus*, devil, or witch) vanished—at least from academic discussion—in Europe during the era of Enlightenment, when such explanations were identified as superstition. From a medical point of view, the evil was assumed to be caused rather by bodily processes such as indigestion,[74] or "stagnation of the blood."[75] Later, within the framework of psychoanalytic reasoning, Ernest Jones understood the nightmare as the expression of the deepest mental conflict, namely incest desires and their repression.[76] In contrast to this concept, Vinchon gave a psychosomatic interpretation of the phenomenon[77]:

> Suffocation accompanied by anxiety is due at the time to the mechanical compression of the thoracic organs by the air pocket of the air swallower and to irritation of the pneumogastric and vagus nerve centers, of which the experimental excitation…provokes a spasm of the bronchiae and a vasodilation which tends to interdict the movement of the air. Concomitant sexual erethism is due to the extension of this nervous excitation to the whole parasympathetic or autonomic system, of which the pneumogastric as well as the sacral nerves form a part. Here the intervention of the psychism appears to be quite a secondary fact; the Freudian repression only throws light upon the more or less picturesque details; it by no means clarifies the mechanism of the phenomena. If it were otherwise, the dream of incubus, instead of coming at almost constant times—those of aerophagic dreams—would be reproduced no matter what hour of the night. But the patients themselves inform us that their other nightmares reproduce quite different pictures.

It was only after the identification of REM and NREM as two different states of sleep that the original symptom complex of

an incapability to move, associated with anxiety, was split into two different disorders. The diagnostic system of the Association of Sleep Disorders Centers subsumed *incubus* under the diagnostic category "Sleep terror," separate from the category "Dream anxiety attacks (nightmares)."[20] In the revised classification system from 2005 the term *incubus* was canceled. Components of the historical symptom complex appear now in three different categories, (i) Recurrent Isolated Sleep Paralysis, (ii) Sleep Terrors, and (iii) Nightmare Disorder.[27]

Pavor Nocturnus—Sleep Terrors

As an observable disorder of infant sleep, *pavor nocturnus* or sleep terror was known already in the Antiquity. Since the 17th century it was mentioned in medical textbooks.[78] The first monograph on sleep terrors in children by the Saxonian doctor Hesse appeared in 1845.[79] He gave a clear description of pavor attacks and separated them from nightmare and sleepwalking. The victim of the attack, which usually starts one or two hours after bedtime, is in panic and does not recognize its environment. The attack starts abruptly, has a duration of 15 to 30 minutes, and comes to an end only slowly. Many children are unable to report what was horrifying them. Based on a series of clinical observations, Rey (1897) assumed adenoid vegetations as the main cause for nightly attacks of pavor.[80] Comparable observations were made earlier by Warrington Haward, at that time a surgeon to London's Hospital for Sick Children, who observed disappearance of what he called "nightmare" after the removal of the tonsils in four children.[81] Braun (1896)[82] regarded the disease as a form of neurasthenia, defined as an increased irritability of the nervous system. He emphasized educational measures for its prevention, medication (bromides, chloral, chinin) in severe cases only, and warm or tepid baths. Much later, in the EEG era of sleep medicine, it was established that somnambulism and night terror arise out of deep NREM sleep and both represent disorders of arousal.[83] Fisher et al.[84] performed clinical studies in which they interviewed subjects, who had actually a terror episode, for any mental content that preceded the event. In many cases, it seemed probable that the night terror episode was a reaction to the mental content of the preceding deep delta sleep phase; however, it was also shown that night terrors could be elicited artificially by external stimuli such as sounding a buzzer. It should be mentioned that subjects in this latter study were young adults, not children, who have the highest prevalence for sleep terror.

MOVEMENT DISORDERS

In contrast to motor parasomnias, sleep related movement disorders "are primarily characterized by relatively simple, usually stereotyped, movements that disturb sleep or its onset."[27]

Anxietas Tibiarum—Restless Legs

Restless legs, an unwanted motor phenomenon which may impede sleep onset, has been known since Willis (1684)[85] in the medical literature. The full clinical picture, however, was only described by the Swedish neurologist Ekbom in 1945, who also presented his own case series of afflicted patients.[86] What is called restless legs syndrome (RLS) today was designated in the earlier medical literature as *anxietas tibiarum*.[24,26,87] The German physician Melchior Adam Weikard quoted different causes of the disease[88]:

> Actually, restlessness, of which we are speaking here, means those so-called anxietas tibiarum (unrest of the calf) of Astruc and Sauvages: namely that uncomfortable state with which men and women are tainted, especially those with blood loss and gout, or those fatigued, who in the evening are barely able to hold their calfs for a minute in the same position or at the same place, due to a troublesome sensation which seems to be relieved somewhat by the restless movements, until they are removed by lying in bed. (p. 215)
> (authors' translation)

Throughout the 19th and 20th century, the symptom pattern of anxietas tibiarum was obviously known to neurologists such as Romberg,[89] Wittmaack and Gilles de la Tourette, Bing, and Oppenheim, who all have mentioned the disorder in their textbooks. When Moritz Romberg (1840) discussed hyperesthesia of the nerves which are connected to the muscles ("*Muskelgefühlsnerven*") he wrote[89]:

> While the distribution of sensible nerve fibers in the voluntary muscles is demonstrated by anatomical studies, the daily observation offers the proof that the muscles are in the possession of sensation of a peculiar character which, in the healthy state, presents itself after strong movements as a feeling of fatigue (*Lassitudo*). This peculiarity also maintains effective in hyperesthesia, as so often preceding the onset of diseases, especially febrile ones, or accompanying other affections, most frequently the hysterical one. In the latter one notices frequently a feeling of anxious restlessness in the legs, especially in the lower legs and feet, which the sufferers don't know how to get rid of, in their own words. They try to get relief by changing the position—but in vain—a phenomenon which has been called by older nosologists (*Astruc, Sauvages*) anxietas tibiarum. (p. 85)
> (authors' translation)

Duncan (1854)[90] and Levick (1862)[91] both reported cases of the disorder in association with pregnancy, an association which is well established now. As effective treatment they used opioids and iron, treatment options which are still in use today. However, although they were obviously dealing with the same symptoms as the neurologists mentioned above, they classified the disorder as a mild form of chorea. Levick explained the terminology as follows[91]:

> The cases correspond closely to the condition known to the earlier writers as *anxietas tibiarum*, and to them the term *scelotyrbe*, employed by Galen, and which is believed by many to have been used by him as synonymous of our chorea, corresponds in its strictest etymological meaning—To σκελος limb, ή τυρβη restlessness. (p. 46)

Jactatio Capitis Nocturna—Rhythmic Movements

Rhythmic movements in sleep, or nocturnal jactations were included in Frank's classification of diseases.[25] These movement disorders preferentially occur in infants and children. However, more detailed reports on rhythmic movements during sleep appeared in the medical literature only much later, beginning with an impressive case report of nocturnal rotary movement read before the New York Medical Society by Mary Putman-Jacobi (1880),[92] one of the early women in medical science. The incidence occurred in a healthy boy at the age of 18 months[92]:

> The mother then noticed, that after the child had been asleep for a couple of hours, he would turn over on his right side, drawing the right arm above his head, and applying the left hand over the left ear. Once in this position, he would begin to oscillate his head on the pillow from right to left, in a perfectly rhythmical manner. The oscillation would be maintained for about half an hour, and then the child slept quietly again. From the time this phenomenon was first observed, no night passed without its occurrence; but for the first six months, the rotary movements were not very rapid—did not last long—and thus did not attract any great attention. They were ascribed to a morbid habit of no special significance. During the last year, however—thus ever since the attack of scarlatina—the oscillation has increased in rapidity, in duration, and even in extent. (p. 390)

This phenomenon was again discussed by the Society of Internal Medicine and Pediatrics in Vienna where Zappert had reported on head banging in children.[93] He suggested that the incident is most similar to other stereotypes and habits which are common in children at this age. The question whether the incident could be an equivalent of masturbation was raised but rejected. Finally, it was noted with regret that the physiology of sleep is not developed enough to allow to determine the depth of sleep at the time of the incident. At the same time, Cruchet,[94] who denoted the incident as tics, differentiated between those which occur selectively at sleep onset and those which occur during sleep. The latter ones were seen by him as sleep habits, comparable to other sleep habits as, e.g., bruxism. The largest early series of 15 cases was published by Stier.[95] In the majority of cases (75% to 80%), banging of the head appeared in the first year of life, in line with what Kleitman[16] found when he had reviewed other cases from the literature. From the early observations, it was less clear at which age the symptoms disappear. In a few cases they occurred still in adolescence or even adulthood.

SLEEP-RELATED RESPIRATORY DISORDERS

It may seem surprising that sleep-related respiratory disorders, which are now worldwide the most prominent sleep disorder, came into the focus of medical observations and care only recently. While snoring (*rhonchus*) and *stertor* (loud snoring) had already been mentioned in classical Greek and Roman medical treatises, one of the first medical dissertations on this topic was published by Alberti and Lust in 1745.[96] These authors described quite detailed anatomical risk factors such as corpulence and a short neck, as well as other factors which impede the airway passage during sleep. However, reports on respiratory pauses (*apnea*) during sleep were rare before the 19th century. Even Charles Des-Alleurs, a French medical doctor, who propounded in his *Apnéologie méthodique* a classification schema for all respiratory disorders, missed sleep-related apneic events.[97] Some later doctors, who had observed repeated apneic pauses in sleep, mostly in corpulent persons, referred to the description of fat Joe, a sleepy boy in Charles Dickens' *The Posthumous Papers of the Pickwick Club* from 1836, and coined the diagnostic term Pickwick syndrome.[98] Reports on sleep-related breathing disorders were rare, however, until the middle of the 20th century.[99–101]

The first polygraphic recordings in Pickwickian patients, which typically show a combination of corpulence, daytime somnolence, and respiratory pauses in sleep, were performed in the 6th decade of the last century. A detailed analysis of these publications was given by Lavie.[102] It should be mentioned that first kymographic registrations of repeated respiratory pauses in sleep were made by the Italian physiologist Mosso[69,103] in a 70-year-old male subject who was in good health. Mosso assumed that the apneas were the result of a "luxury ventilation," a phenomenon which was familiar to him by his extensive physiological studies on respiration in the high Alps.

Concerning respiratory disorders in the sleep of infants and children it may be of interest, that in the pediatric literature they were mentioned first in connection with nightmares[104] or sleep terrors.[80] These authors assumed that an obstruction of the respiratory tract during sleep results in a slow intoxication by carbonic acid, which gives way to the feeling of suffocation and the terror attack. Henoch, who had made additional observations on children suffering from sleep terror, reported on the curative effect of the elimination of enlarged tonsils and adenoid vegetations in afflicted children.[105] However, it was only in the second half of the 20th century that sleep apnea as a sleep-associated disorder has been recognized in infants and children.[106]

While reports on therapeutic interventions are very rare in the historic literature, general advice was given to avoid a supine position in sleep, which favors snoring and mouth breathing. In a few early cases, resection of parts of the soft palate successfully eliminated obstruction of respiration in sleep.[104,107–109] A breakthrough in therapy came in 1981 when Sullivan et al.[110] were the first to treat sleep apnea mechanically by continuous positive airway pressure, a method which soon became the treatment of choice. Increased awareness of sleep-related respiratory disorders was backed by research on the pathophysiological mechanisms and the development of adequate treatment facilities in the last five decades.

We have speculated elsewhere whether the discrepancy between the rare reports on sleep apnea before the middle of the last century and the actual high incidence of the disease may be co-determined essentially by two population-wide factors, age and body mass.[69] Census date in industrialized countries show an increase of older persons (for the United States see https://www.census.gov/dataviz/visualizations/055/), who are known to have

an increased risk for developing sleep apnea.[111] In addition, for the last 150 years a secular trend of increased body height has been documented.[112,113] While adult height has largely stabilized now,[114] weight continues to increase. It is quite probable that these trends led to changes of the upper airway anatomy with negative consequences for the respiratory system in sleep, since a close association between anatomical preconditions and the risk for sleep apnea is well established.[115] If this reasoning is true, one would expect an increased population risk for obstructive sleep apnea in those societies which display these anthropomorphic trends.

SLEEP DISORDERS IN INFANTS AND CHILDREN

From the 15th to the 19th century, sleep disorders were rarely discussed under the aspect of age or development, and references to disturbed sleep in infants and children are rare for this epoch. One of the first treatises on diseases of infants was written by the Persian physician Al-Razi, Muhammad b Zakariya', or Rhazes (c.854–925) and published in Latin in 1544. One of the diseases, which he described, was sleeplessness in infants, caused by tainted milk. As treatment he prescribed to rub in the head, the nostrils and the epigastrium with special oils and to apply syrup from the Poppy.[116] For centuries, sleep terrors or *pavor nocturnus* was the leading sleep disorder in the emerging pediatric literature.[117–119] Roesslin's book[119] had also chapters on sleeplessness and nightmares in infants and gave advice how best to avoid such disorders. Other sleep disorders, which were observed in infants and children were insomnia and nightmares. Sleepwalking, which was first described in adults, was mentioned in children only since the 18th century,[120] and sleep related rhythmic movement disorders, like body rocking or head rolling, appeared in the pediatric literature only at the beginning of the 20th century.[93,94] Sleep enuresis, or *enuresis nocturna,* was first mentioned in the medical literature on children in the second half of the 17th century,[121–123] and later became the pediatric sleep problem with the highest number of medical references, probably due to the fact that bedwetting could be managed finally quite effectively by newly developed behavioral techniques[124] and by drugs.[125]

During the 19th century, information about sleep disturbances across development concerned mainly children and came from the medical domain, usually through clinical observations of single cases. Clinical descriptions referred sleep disturbances mainly to CNS pathology or physical diseases. Relative few attention was given in textbooks and publications to children's sleep problems, except episodic phenomena like sleep terrors and enuresis. In the 20th century, pediatricians became more concerned about children's sleep problems, linking them to the particular aspects of pediatric practice at that epoch. New approaches were undertaken by neuropsychiatrists.[126,127] Attention was given to the parent-child relationship and child management, which allowed understanding some aspects of child sleep disturbances which remain quite pertinent today. Another reason for the growing interest in the development of sleep was that pediatricians adapted new techniques to measure the course of sleep in infants and children, either by repeated electrical stimulation[128] or by actimetry.[129] In the second half of the century, the focus shifted toward the study of the first years of life, i.e., studying newborns and preterm infants. In the early 60s, the sleep medicine of the early stages of development received strong impulses from neurophysiological studies conducted in Europe by the groups of Dreyfus-Brisac[130,131] and Prechtl,[132,133] and in USA by Parmelee et al.[134] and Ellingson.[135] The physiological studies of newborn and preterm infants allowed to ascertain both the developmental steps of maturation of the CNS and the impact of pathology (mainly neurological and metabolic), consisting in sleep state disorganization and frequent spontaneous awakenings.

In the 1970s, sleep researchers began to study SIDS (sudden infant death syndrome), a pathology which often takes place during sleep in infants, mainly between 2 and 6 months of age, a time of important sleep modifications. Polygraphic recordings, including respiration and cardiac rhythm, were performed in those infants who escaped death and in siblings to establish risk. Several physiopathological studies evaluated the role of apneas during sleep; however, finally this factor was not considered crucial for SIDS. On the other hand, some researchers have put forward the hypothesis that the awakening mechanism is deficient and does not allow the infant to escape from what results eventually in death during sleep.[136]

Pediatric pathology derived benefit from the joint evaluation of physiological activities, like endocrinological, and polygraphic sleep recording. Among these, the importance of the evaluation of growth hormone secretion during sleep for the prediction of successive infant growth was underscored.

The *sleep disturbances not related to other pathologies*, which was previously a matter of single case studies, was, from the 1970s on, investigated in a more systematic manner.

Parental behavior was analyzed by psychological as well as sociological approaches.[137] The role of practices around sleep, in particular for sleep onset and night awakenings, was shown in different contexts both in the USA and in Europe, and the socioeconomic status was taken into account for some sleeping conditions, e.g., cosleeping. Conversely, several studies investigated the consequences of child sleep disturbances on the family (family distress).

A systematic approach to the child sleep disturbances took advantage from surveys performed both in Europe and in the USA. Some interesting results were reported, such as the scarce specific demand in respect to sleep problems in both public and private health centers. On the other hand, difficulties with falling asleep, and night waking were often reported in the questionnaire studies.[138] Those surveys showed also a high proportion of children taking psychotropic drugs. The pharmacological treatment was used in the last decades of the 20th century, in particular to treat parasomnias and narcolepsy.[139] Parallel to research performed in adults, sleepiness became a topic of intense investigation also in children and adolescents, in particular in regard to potential consequences for behavior and school performance.[140]

CIRCADIAN RHYTHM SLEEP DISORDERS

Daily variations in physiological functions have been studied since the early 17th century,[141,142] and likewise observations

were made on periodicities in the time course of different diseases, including unusual alterations of sleep and wakefulness.[143,144] A sort of thesaurus of any periodic changes in the life of healthy and ill persons, collected from medical publications, appeared in 1836.[145] Sections of the book are devoted to sleep and waking, daily rhythms, periodic illnesses and their relationship to the time of day, and finally instructions for the appropriate time to give medicine. Beyond, the potential deleterious effects on sleep of sleeping or waking at unusual hours, required by profession, was discussed by Becquerel in 1873 in a treatise on medical hygiene[146]:

> There are occupations which cause serious inconveniences by the sleep deprivation they entail. This holds for night-watchmen in some countries, the watchmen of our hospitals, men appointed to public safety, nurses; all of them often experience bad effects of shifting the hours that are usually devoted to sleep. A sleep of adequate duration is far from providing the same rest depending on whether it is caught during the day or at night. In the first case, its positive influence is much smaller, and we must attribute this result to the light and noise which are stimuli whose effects are being felt. In some trades the same inconveniences exist: bakers work at night, the garbage collectors do the same, many of them cannot get used to this system change. Sailors sleep little in general; quarter watches at night are a very painful system, and many of them have trouble to get used to it. (p. 835)
> (authors' translation)

An important innovation for the study of the rest-activity cycle was made by the Viennese biologist Szymanski, who developed actimetric devices to measure activity continuously across 24 hours in all sorts of animals, and in human babies.[4] This technique allowed him to differentiate between mono- and polyphasic sleep-wake patterns in different species, and also between day-active animals, which use light and night-active animals which use odor for orientation. Szymanski assumed also a relationship between the duration of rest and the depth of sleep. This made the method popular for to study sleep in infants[129] and adults[147] in the pre-EEG area. There was a revival of the method when miniaturized portable actimetric devices became available in the late 1980s, which were used for circadian research[148] and sleep medicine.[149,150]

Systematic chronobiological research in animals and human beings started in the middle of the last century. Key studies were performed by the groups of the physiologist Jürgen Aschoff in Germany and the biologist Colin Pittendrigh in the United States. They demonstrated the independence of biological timekeeping systems from external signals and studied the interaction of the rest-activity cycle with body temperature, endocrine, and other bodily systems. Next, the interaction of internal pacemakers ("biological clock") and external stimuli (*Zeitgeber*), such as light, was studied. Research of circadian rhythms expanded rapidly into neurophysiology when the N. suprachiasmaticus (SCN) of the hypothalamus was recognized by lesion studies as the central locus of the circadian timing system in the year 1978.[151] This finding led to new priorities in circadian research, (i) the interaction between SCN and other brain systems and especially those which are involved in sleep-wake regulation, (ii) the interaction between the SCN and external *Zeitgebers*, mainly via the visual system, and (iii) the molecular genetic organization of the biological clock. The interaction between sleep and circadian rhythms was studied intensively in the following years, starting with polygraphic sleep recordings under conditions of temporal isolation.[152,153] Results of experimental studies were integrated into a theoretical frame by the most influential two-process model of sleep regulation.[154]

The results from basic research fostered a new look on sleep pathologies: a disruption of sleep could either result from a disturbance of sleep regulation itself, e.g., an increased rate of arousals, or from a misalignment between sleep and the circadian system, as e.g., in shift work. While these latter disorders were for the first time in the history of sleep medicine classified in the first version of the diagnostic system of sleep disorders as "disorders of the sleep-wake schedule."[20] This new diagnostic category of disorders, called "circadian rhythm sleep disorders," is fully established now. Sleep-wake disorders are expected to gain in importance in the future in high-tech societies with an increasingly large service sector.

FREQUENCY OF SLEEP DISORDER REFERENCES THROUGHOUT 500 CENTURIES

The number of medical and other publications on the different sleep disorders shows some systematic trends across the last 500 years. The number of publications on sleep disorders follows an exponential growth curve, with 25 references for the time interval 1500–1549 and 12,281 for the time interval 1950–1999 (**Table 1**). **Figure 1** displays the relative frequencies for each diagnostic category and time interval. The figure shows that "parasomnias" was the leading diagnostic category between 1500 and 1900, followed by a sharp decline of the relative frequency in the 20th century. Insomnia is the second most frequent diagnosis, however with a dip between 1750 and 1850. Hypersomnolence holds rank three, with a local maximum in the first half of the 20th century. At this time, narcolepsy has been established as a new diagnosis beside the traditional forms of hypersomnolence of central origin. Restless legs syndrome, although known as *anxietas tibialis* since the middle of the 17th century, was mentioned rarely in the medical literature during the following centuries. The number of RLS references began to rise only late in the 20th century. The ranking of diagnoses changed quite dramatically in the second half of the 20th century when obstructive sleep apnea took over rank one in absolute numbers (**Table 1**), corresponding to 44% of all sleep disorder diagnoses for this time interval (**Figure 1**).

CONCLUSIONS

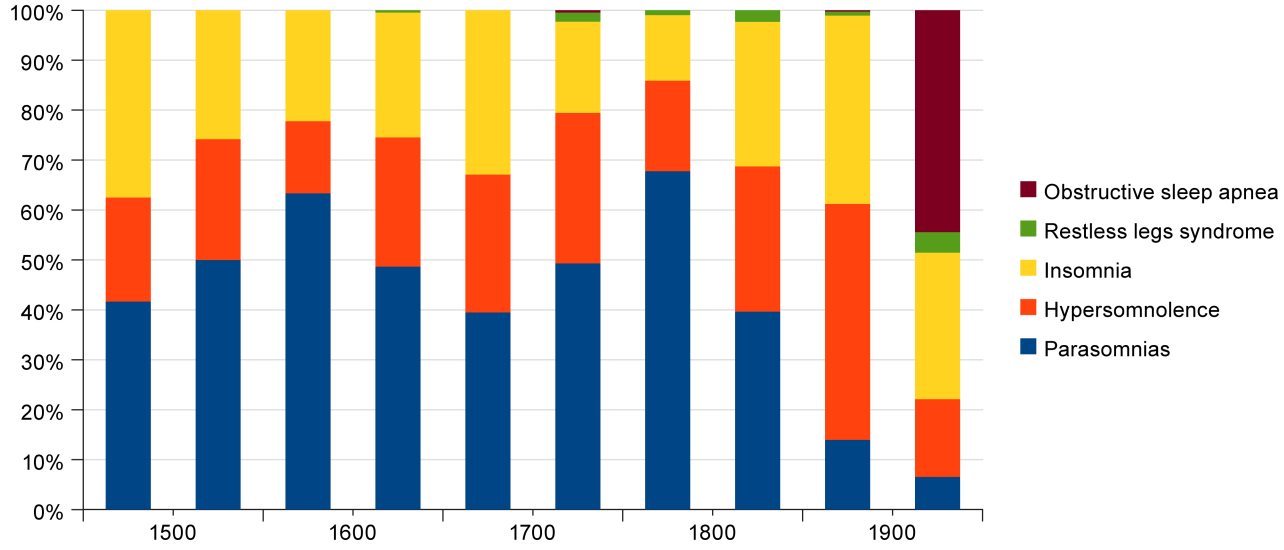
To study "*the sleep of others*" was formulated as a program by Kronthal (1907)[155] when experimental sleep research was still in its infancy, while the same slogan was used 100 years later as

Table 1—Number of references for each of five categories of sleep disorders between the years 1500 and 2000.

	Time Interval									
	1500–1549	1550–1599	1600–1649	1650–1699	1700–1749	1750–1799	1800–1849	1850–1899	1900–1949	1950–1999
Diagnoses										
OSA	–	–	–	–	–	1	–	–	3	5,457
RLS	–	–	–	1	–	4	4	13	9	506
Insomnia	9	16	20	56	50	40	55	162	427	3,601
Hypersomnolence	5	15	13	58	42	66	76	163	535	1,915
Parasomnias*	11	32	57	110	62	109	287	229	158	802
Total	25	63	90	225	154	220	422	567	1,132	12,281

Time was segmented into 10 intervals of 50 years each. Data were drawn from the literature data bank of one of us (HS). The references for the time interval 1950 to 1999 were drawn from a Medline search, supplemented by references from our own literature data bank, since Medline references are incomplete for the first years of this time interval *Parasomnias were defined as the sum of the diagnoses sleepwalking, sleep terrors (pavor nocturnus) and nightmare (incubus).

Figure 1—Relative frequency (percent values) of references of 5 categories of sleep disorders from 1500 to 1999.



Each century is split into two blocks of 50 years each.

a quintessence by Kroker (2007),[156] without having knowledge of the earlier source, when he traced the historical development of research on sleep and its disorders. Until the early 20th century, the recognition of sleep disorders was limited to those which could be reported by the afflicted person, mainly insomnia, or observed by others either during the wake hours, e.g., severe sleepiness, or during the dark hours, e.g., sleepwalking and sleep terror. Other sleep-wake disorders remained unrecognized until recently, either because instruments to measure physiological functions in sleep were non-existent or because the underlying physiological mechanisms were not sufficiently known to appreciate pathological deviations. This is especially true for sleep related breathing disorders. Finally, circadian rhythm sleep disorders are a class of sleep-wake disorders which came into focus only when circadian physiology was developed in the second half of the last century. An increasing number of such disorders can be expected in the future due to the way of life in technically highly developed societies with global interactions around the clock.

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