Lung Biology in Health and Disease Volume 220
Executive Editor: Claude Lenfant

Narcolepsy and Hypersomnia

edited by
Claudio L. Bassetti
Michel Billiard
Emmanuel Mignot

Narcolepsy and Hypersomnia

LUNG BIOLOGY IN HEALTH AND DISEASE

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Narcolepsy and Hypersomnia

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Introduction

From a medical viewpoint, narcolepsy (and its corollary hypersomnia) is a very interesting disease, not to say a fascinating one. It is also a mysterious disease which may not receive the recognition it deserves, unless of course one is affected by it! Nonetheless, the medical history of this disease is already long and has been superbly traced by one of the editors of this monograph (1). Briefly, the first description of the symptoms was reported in 1877 in Germany, but the name "narcolepsy" was given by a French physician in 1880. Interestingly, the name is derived from Greek, and it means "seized by somnolence." However, it is only in the mid-nineteen hundreds that the tetrad of the disease was described: excessive daytime sleepiness, cataplexy, sleep paralysis, and hypnagogic hallucinations.

Perhaps one of the most intriguing aspects of the evolution of our knowledge of narcolepsy is that it was first thought to be some sort of psychological disorder or an escape from reality. Eventually it was recognized that it is a somatic disease. However, many questions emerged regarding the cause: Is it a neurochemical dysfunction? Is it an autoimmune disorder? Is it a genetic condition? The reality is that each of these determinants is playing a role in the development of the disease. As often happens in medical sciences, it is research on the possible treatment of another disease, obesity, which led to the discovery of two peptides expressed in the hypothalamus and named "hypocretins." The discovery of these peptides and of their receptors opened the door to the most current understanding of narcolepsy.

This volume, *Narcolepsy and Hypersomnia*, does not complete the journey of narcolepsy, but it gives the most complete and up-to-date presentation of the disease, its manifestations, its pathogenetic pathways, and its current treatments.

Narcolepsy is not a rare disease. All over the world, it affects thousands of patients who will eventually benefit from the work of the many experts working on it. The editors, Drs. Claudio Bassetti, Michel Billiard, and Emmanuel Mignot deserve much commendation for organizing this book and calling on international experts. In many ways, this volume superbly illustrates the reasons for the initiation of this series of monographs, Lung Biology in Health and Disease: to inform, to educate, and to stimulate!

As the chief editor of this series, I want to express my thanks and appreciation to the editors and contributors for the privilege to introduce the volume to our readership.

Claude Lenfant
Gaithersburg, Maryland, U.S.A.

Reference

1. Mignot E. A hundred years of narcolepsy research. Archives Italiennes de Biologie 2001;139:207–220.

Preface

It has been almost 30 years since the First International Symposium on Narcolepsy was held in La Grande Motte (France) in 1975, under the leadership of William C. Dement, Christian Guilleminault and Pierre Passouant. In this first symposium, a milestone in the area of narcolepsy, the basis of the questions we are still exploring today were laid out. It was recognized that narcolepsy symptoms were intimately related to rapid eye movement (REM) sleep abnormalities. A natural animal model of narcolepsy, canine narcolepsy, was first reported. The first epidemiological and family studies of the condition were described. New classes of pharmacological agents including tricyclics and gammahydroxybutyrate were found to be useful in the treatment of cataplexy, leading to a better codification of narcolepsy therapies.

The discovery of the HLA-narcolepsy association in 1983 rekindled interest in the condition and raised the possibility of immune abnormalities in the disorder. Several international symposia on narcolepsy were then held, including one at Stanford (USA) in 1985, one in Oak Park (USA) in 1989, one in Paris (France) in 1993 and one in Tokyo (Japan) in 1994.

In 1999, the positional cloning of the canine narcolepsy gene and its identification as the hypocretin (orexin) receptor 2 gene was another milestone in the field. A mouse knockout model for the hypocretin gene was also found to display narcolepsy-like symptoms. In 2000, these discoveries were followed by the report that most cases of human narcolepsy-cataplexy are associated with hypocretin deficiency. Together with the HLA association, these results suggest that narcolepsy may be an autoimmune disorder targeting hypocretin-containing cells in the hypothalamus.

These discoveries are leading to new diagnostic procedures, for example the measurement of cerebrospinal fluid hypocretin-1 levels, and have rekindled research

interest in brain mechanisms hypersomnia. New animal models and novel therapeutic strategies targeting the immune or the hypocretin systems are being developed. Improved epidemiological surveys, a better definition of the narcolepsy spectrum, the finding of hormonal and metabolic abnormalities in narcolepsy, the identification of non-HLA genes involved in narcolepsy are other areas under active investigation.

The explosion of research in the area of narcolepsy and hypocretin mandated the need for an international body to meet, discuss and report on these new developments. Switzerland, a country with a long tradition in sleep research and medicine, was chosen for this event. The event will take place at the Centro Stefano Franscini in the serene and picturesque surroundings of Monte-Verità, Ascona (Ticino, Switzerland).

In the spirit of communicating the great changes that have occurred in the field, we felt it was time to publish an updated monograph reporting on Narcolepsy and Hypersomnia. We took great care in inviting leading experts who could cover all aspects of narcolepsy and hypersomnia in a comprehensive textbook to be used by clinicians and researchers alike as a reference book for many years to come. We hope you will enjoy the resulting book, *Narcolepsy and Hypersomnia*, published by Informa Healthcare and the series editor Claude Lenfant.

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Contents

1
Historical Aspects of Narcolepsy

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It is the strong opinion of this author that research on narcolepsy and the diagnosis and treatment of patients afflicted with narcolepsy have a value not only for narcolepsy patients but also a value beyond a sole concern about the illness. The following brief history will support this opinion.

We know that insomnia symptoms and other types of disturbances such as sleepwalking and night terrors have been a problem for humans almost certainly since the dawn of history. They are mentioned in the writings of Aristotle and others. However, the first clear description of a specific sleep pathology was published by Jean-Baptiste Edouard Gelineau (1828–1906) in 1880. Several patients who surely had narcolepsy had been described previously by others, but Gelineau realized that the characteristic symptoms almost always clustered and bestowed upon them the name "narcolepsy." The Gelineau report (1), which appeared in the Gazette des Hospitals, describes how emotions influence the onset of sleep attacks and how some attacks were quite literally falling down. Gelineau also felt that narcolepsy should be regarded as an autonomous disease and should not be confused with epileptic seizures.

Narcolepsy research has revealed additional characteristics of the illness beyond the classical tetrad. Nonetheless, the four features that comprised the syndrome in the original description are as follows (2):

1. Excessive and persistent somnolence: daytime sleepiness at inappropriate times, or sleep attacks, sudden urges to sleep, without regard to either the amount or the quality of prior nighttime sleep.
2. Cataplexy: episodes of partial or general muscular weakness induced by emotions, such as laughter, anger, or surprise.
3. Hypnagogic hallucinations: vivid, realistic, and sometimes frightening auditory or visual perceptions which occur at sleep onset.
4. Sleep paralysis: episodes of temporary inability to move or speak, which occur while falling asleep or awakening.

There are other consistent features of narcolepsy as well as exciting new research on neurotransmitter systems in the brain which will be described throughout this book.

I. Pre-REM Years

The illness of narcolepsy, particularly attacks of cataplexy, though not highly prevalent, seems sufficiently interesting that it should not have been so generally ignored. On the other hand, narcolepsy did eventually capture the interest of a few individuals. A large case series was accumulated at the Mayo Clinic, first reported by Daniels (3) and subsequently by Yoss and Daly (4). Bedrich Roth in Czechoslovakia also focused on narcolepsy and accumulated a large number of cases. He published an early monograph on narcolepsy and the second edition was finally translated into English in 1980 (5). In spite of the clarity of the Gelineau description of a syndrome, the inability to conceive a single mechanism that could parsimoniously account for complete muscular atonia triggered by strong emotion on the one hand, and relentless sleepiness on the other, fostered great misunderstanding and misinterpretation. For example, the huge numbers of individuals who survived the encephalitis epidemic of 1917 were labeled narcoleptics. With a turn-of-the-century Freudian emphasis on hysteria and conversion, the impression grew that the cataplectic attacks often triggered by anger were a hysterical defense against aggressive behavior. Many health professionals, including the very eminent British neurologist, Sir Russell Brain, continued to believe that narcolepsy was a form of epilepsy. Finally, Yoss and Daly diagnosed "independent narcolepsy" when patients complained only of sleepiness.

II. The Discovery of REM Sleep

It would probably be quite accurate to say that the narcolepsy syndrome was destined to remain a mystery unless and until REM sleep with its unique physiology was discovered and thoroughly described. As recently as 1952, rapid eye movements during sleep were not known to exist. Even after the first observations (6,7,8), REM periods were considered a form of light sleep. Moreover, the initial interest in REM sleep was mainly its relation to vivid dreaming demonstrated by the very high percentage of detailed dream recall when volunteers were awakened from REM periods.

The discovery of REM sleep in cats (9) with the associated EMG suppression, and Michel Jouvet's elegant studies of muscular atonia and its brain stem substrates also in cats (10,11) clinched the concept of the duality of sleep. According to this concept, REM periods constituted an independent state of being associated with muscular paralysis, vivid hallucinatory dreaming and activated EEG.

III. Sleep Onset REM Periods

The occurrence of sleep onset REM periods in a patient with narcolepsy was reported by Vogel in 1960 (12). A larger group of nine patients was reported by Rechtschaffen et al. a few years later (13). The abnormal occurrence of REM sleep at the onset of sleep was the obvious explanation for the occurrence of hypnogogic hallucinations and sleep paralysis in narcoleptic patients. Several studies in normal animals showed that REM sleep was associated with an active inhibition of alpha and gamma spinal motor neurons (14). This inhibitory process was found to be initiated by centers in the pontine tegmentum.

The evidence of a REM sleep abnormality in narcoleptic patients in terms of sleep onset REM periods led to the conclusion that cataplexy was the initiation of REM atonia in the waking state triggered by strong emotion. This was confirmed by recording one or two daytime naps in a large number of patients complaining of sleepiness (15). Those who also complained of cataplexy had sleep onset REM periods and those who did not complain of cataplexy also did not have SOREMPs. Subsequently, it was realized that most of the sleepy patients *without* cataplexy were suffering from obstructive sleep apnea.

The large number of patients accumulated in the sleep onset REM periods/cataplexy study were identified and recruited by placing a small advertisement in the *San Francisco Chronicle* daily newspaper. As these individuals came forward, it was found that none had a previous diagnosis of narcolepsy and, of course, none had been properly treated. The Stanford group was thus in the position of being responsible for the clinical management of several hundred patients with narcolepsy. In order to make this daunting task practical and feasible, a special narcolepsy clinic was launched. The clinic soon failed financially because patients generally were unable to pay for the diagnostic testing to demonstrate sleep onset REM periods in addition to the office visits.

This first experience of clinic dedicated to the diagnosis and treatment of one sleep disorder was the inspiration for a renewed effort to establish a clinic and the formal launch of the world's first full-service sleep disorders center diagnosing insomnia, sleep apnea, narcolepsy and other sleep disorders at Stanford in the summer of 1970. One may speculate that if the experiences of the narcolepsy clinic had not taken place and had not been a satisfying mode of clinical practice, the Stanford Sleep Center would never have been launched.

IV. Efforts to Establish Prevalence

The majority of the patients referred to the Stanford Sleep Disorders Clinic were thought to have narcolepsy by their referring physicians. This would suggest a much higher prevalence in society than previously thought. In view of this, we decided to try to establish a reliable population prevalence for narcolepsy in the United States. The first effort involved newspaper advertising. Very large displays were placed in three bay area newspapers (total circulation 1,200,000) requesting persons with certain characteristics to respond. The study had controls and a rationale for arriving at the final result which was a "conservative estimate of the number of narcoleptics (sleepiness plus cataplexy) in the USA is 100,000 (.05%)." We tried to publish our results and received a great deal of critical review from epidemiologists, along with a series of rejections. Since we eventually physically examined and tested the survey respondents, we were fairly confident of our results. However, because of the continuing skepticism, another study was carried out in the Los Angeles area utilizing television broadcasting with a film depicting sleep attacks and cataplexy. The second study allowed a conservative conclusion that "there are 130,000 (.067%) Americans who suffered from narcolepsy." Studies since this time have raised the figure to about 200,000. We were also unable to publish the results of the second study. Both are reasonably thoroughly described in the abstracts (16,17).

V. Discovery of Canine Narcolepsy

The Stanford staff kept wider records of cataplectic attacks for educational purposes. These were exhibited at an American Medical Association convention in San Francisco in 1972. Seeing the film of human cataplexy, one neurologist informed the Stanford group that a Doberman pinscher with the same behavior had been observed at the University of California, Davis, School of Veterinary Medicine. When the attending veterinarian was contacted, it was learned that he had sacrificed the dog because it suffered from "intractable, untreatable epilepsy." However, he had made a movie of the dog's "seizures" which he sent to Stanford. In the film, global muscular atonia occurred which closely resembled a cataplectic attack whenever the dog approached a bowl of food.

Subsequently, movies of human cataplexy made by the Stanford group, together with the movie of the UC Davis Doberman pinscher collapsing were shown at an American Association of Neurology meeting in Boston in 1973. A neurologist at this meeting reported that he was aware of a dog which showed these periodic collapses. The dog, a French poodle, was alive and well in Saskatoon, Saskatchewan, and the owners were persuaded to donate her to the Stanford Sleep Center. When the dog arrived she was quickly proven to have classical REM atonia/sleep onset REM periods and possibly to be excessively sleepy. The latter was more difficult to establish because excessive sleepiness is primarily a subjective report.

Reasoning that if one dog with narcolepsy existed there had to be others, I undertook a national search by giving lectures at every possible location of veterinary schools and animal care centers. My lectures included a meticulous description of canine narcolepsy and were accompanied by movies of canine narcolepsy. Our second narcoleptic dog was also a French poodle. From 1974–1975, we received a number of dogs from veterinarians around the United States. With considerable difficulty because of inexperience and inadequate facilities, we nonetheless bred male and female narcoleptic canines and whelped the puppies. Sometime in 1976, a litter from male and female narcoleptic Doberman pinschers appeared to be developing narcolepsy. However, the puppies became ill with viral encephalitis and all died. In 1977, a litter of five puppies were successfully delivered from narcoleptic Doberman pinscher parents and around 8 weeks of age, almost on the same day, all puppies developed obvious cataplexy. This litter received enormous media coverage. If we played with the puppies, all would have cataplectic attacks simultaneously. Ultimately a sizeable colony was established at Stanford, and with inbreeding, a heritable form of narcolepsy/cataplexy was established (18,19,20). This colony was maintained for more than 20 years until the narcolepsy gene was isolated by Emmanuel Mignot's group at Stanford in 1999 (21).

As the leading instigator of the early efforts, I am content that the considerable outlay of funds to house and feed a large colony of narcoleptic canines for twenty years has paid off, and paid off quite handsomely, I might add.

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2
English Translations of the First Clinical Reports on Narcolepsy by Gélineau and on Cataplexy by Westphal in the Late 19th Century, with Commentary

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To our knowledge, there are no published English translations of the first clinical reports describing narcolepsy and cataplexy [in French, 1880, in two parts (1), and in German, 1877 (2)]. The first author of this chapter (CHS) previously had the Berlitz agency translate these two reports, and so this 2006 "state of the science" book on narcolepsy is a timely opportunity for presenting in English the original descriptions of narcolepsy and cataplexy. These historic documents richly describe recurrent, self-limited, sleep attacks and/or cataplectic attacks in two otherwise healthy people.

We have some preliminary comments concerning the translations. First, all punctuations and italics come from the original articles. Second, the article by Gélineau on narcolepsy was twice as long as the article by Westphal on cataplexy. Third, we edited the translations slightly in order to eliminate text that had no bearing on the description of narcolepsy or cataplexy. We eliminated 19 phrases or sentences and six paragraphs from the Gélineau reports, and three phrases or sentences and one paragraph from the Westphal report. We indicated the deletions with either ". . ." for the deleted phrases or sentences, or else "(paragraph deleted)." Fourth, the Berlitz translator of the Gélineau report made this comment: "The original French of this two-part article is written in an unusually loose style for late 19th century scientific reports. It is somewhat like a slightly-edited copying of hasty notes on a physician's note pad. Accordingly, it is difficult to render in smooth English; we have in many cases sacrificed esthetics of style for accuracy." Nevertheless, Passouant, who wrote about Gélineau for the narcolepsy centennial, mentioned that "Throughout his life, Gélineau wrote in a clear, alert, and

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easy-to-read style (3)." It is evident that Gélineau astutely identified and accurately named *narcolepsy*, and he wrote an impressive set of descriptions on narcoleptic sleep attacks and their contexts, and he provided a detailed and carefully reasoned differential diagnosis and list of treatments.

We will now comment on certain other aspects of these two reports. (However, at this point the reader may wish to read the translations of the original texts contained in the final section of this chapter before returning to read our comments.)

I. Gélineau's Description of Narcolepsy

Dr. Jean Baptiste Edouard Gélineau (1828–1906) at the outset of his report attributed the initial description of narcolepsy to a Dr. Caffé who had published a case 18 years earlier, in 1862. However, our reading of Gélineau's quotes from Caffé's report would instead suggest the diagnosis of obstructive sleep apnea (OSA) as being more likely than narcolepsy. The case involved a 47-year-old man with "an irresistible and incessant propensity to sleep" that had forced him to resign from his job. He was not reported to have cataplexy, sleep paralysis or hypnagogic/hypnopompic hallucinations. However, he was reported to have "attitude detached; stupor; mental sluggishness; persistent stoutness; effect on overall health," and his face was "puffy." These descriptions are more indicative of OSA than of narcolepsy. Also, in consulting two different thesauruses concerning the word "stoutness," we found the following: One thesaurus had two physical meanings for this word (fatness, sturdiness), and of the 10 physical synonyms listed, nine were closely related to "fatness." The other thesaurus had two physical meanings for stoutness (size, strength), and of six physical synonyms listed, three pertained to fatness. In addition, the use of the word "persistent" to describe stoutness is much more likely to be a comment on an overweight or obesity status than of a strength or sturdiness status. For example, the phrase "a patient is persistently strong" would not be used, whereas "a patient is persistently overweight or obese" would be used. Therefore, Dr. Caffé presumably wished to convey an overweight or obese status concerning his patient when he used the word "stoutness." (One of the coauthors of this chapter—IA—reinforces this conclusion in regards to the word "fort" that describes a person being "overweight" distinctly more so than "strong," both in the 19th century and in the contemporary French language.) Although various treatments did not help Dr. Caffé's patient, a stay at a spa did improve his condition. Is it possible that he lost weight at the spa, which would have had a beneficial effect on his presumed OSA?

Gélineau presents a 38-year-old man with a two-year history of very frequent narcoleptic sleep attacks, totaling up to 200 attacks daily. This man could not speak with Dr. Gélineau for even 30 minutes without falling asleep, and constantly needed his 13-year-old son at his side to keep awakening him, so he could attend to his successful business. A wide array of intense emotional states played a prominent role in triggering his sleep attacks. The description of his initial visit with Dr. Gélineau is a dramatic example. In reading the entire report, a question could be raised as to whether this man—besides his "volatile temperament"—had histrionic personality traits that interacted with his narcolepsy. Gélineau briefly described cataplexy (which he termed falls or "astasia") and sleep paralysis in his patient, but did not comment on the presence of sleep-onset dreaming, dream disturbance, or hypnagogic/hypnopompic hallucinations. He mentioned that

his patient had "excellent night-time sleep, waking only once," which argues against the presence of either disruptive periodic limb movements of sleep or rapid eye movement (REM) sleep behavior disorder, conditions now known to be associated frequently with narcolepsy. Cataplexy was the initial manifestation of his narcolepsy.

Gélineau's patient was a member of the "mutual aid society," and his card bore the diagnosis, "*morbis sacer*," Latin for "sacred disease" in reference to epilepsy, which during antiquity had been considered a divine disorder. Gélineau's male patient reported that his infant child "was conceived in a moment when the illness came over him." Among the various explanations to account for this intriguing comment, the most likely would be either a hypnagogic hallucination or a vivid sleep-onset REM dream, which are common events with narcolepsy that may have accounted for an imagined sexual event. Another possibility is that this man indeed had coitus with his wife while awake that was immediately followed by a sleep attack, and in retrospect he incorrectly recalled the coitus to have occurred during the sleep attack. This patient received many unsuccessful treatments, including bromides, strychnine arsenate, curare, picrotoxin, apomorphine, phosphates, amyl nitrate vapors, hydrotherapy, electricity, and cauterization of the nape of his neck. Gélineau was thus led to comment, "as we both acknowledged that these successes were not in keeping with our mutual efforts, we lost contact, leaving to time and to nature the care of healing or improving this painful neurosis."

II. Westphal's Description of Narcolepsy–Cataplexy

Westphal had two cases that he presented at a Berlin Medical and Psychological Society meeting during 1877 that were then published in the *Archives of Psychiatry and Nervous Disorders* (for which he was an Editor). It is of note that he first chose to speak and write about "larvate epileptic attacks" before he described a patient with excessive daytime sleepiness and cataplectic attacks. Westphal emphasized in italics two aspects of his patient's clinical history: "*He did not lose consciousness during these attacks*," and "persistent *night-time sleeplessness* must be noted." Westphal clearly grasped that the cataplectic attacks involved loss of muscle tone without associated loss of consciousness, and his comment about sleeplessness indicated the presence of disrupted nocturnal sleep that is common (but not mandatory) in narcolepsy. In being the first investigator to describe narcolepsy with cataplexy, Westphal was also the first to describe familial narcolepsy, as the mother of his 36-year-old male patient had also suffered from longstanding sleep attacks and possibly cataplexy that was of milder severity than her son's cataplexy (although "she had been troubled by such attacks frequently earlier on"). Westphal also described repeated sleep attacks in his patient: "At times ... these attacks (viz. cataplexy) do cause the patient to fall asleep. The falling asleep appears, as it were, to be an extension or increase of the attack." The patient would also have sleep attacks in public while "still speaking" or while "strolling around quietly and aimlessly." These descriptions of sleep attacks and cataplectic attacks prove that Westphal correctly recognized and described narcolepsy with cataplexy before Gélineau, although he did not name these conditions, as did Gélineau for narcolepsy in 1880 and Henneberg for cataplexy in 1916 (4). It is noteworthy that only in 1902 a third author (Löwenfeld) confirmed Westphal's and Gelineau's suggestion that narcolepsy with cataplexy represents a "disease sui generis" (5).

III. The Authors

Let us be transported to 1878. The forceful unification of Germany by Prussia's Otto van Bismark has been completed after first defeating Austria and then the French armies during the short 1870 war against Napoleon the third. Germany is a strong but barely united country. France has lost the Alsace and the Lorraine and is a separate continent from Germany both culturally and linguistically. Psychoanalysis is not formally established. Sigmund Freud has not yet completed medical school, but there is growing interest in the unconscious and in psychological explanations for physical disorders. The pioneering work of Jean Martin Charcot's "Leçons sur les Maladies du Système Nerveux" has just been published, introducing the notion of hysteria. Neurology and Psychiatry are still in most countries all but one discipline.

Karl Friedrich Otto Westphal, born in 1833 in Berlin, is the son of a well-known and wealthy physician. After a European medical education that included studies in Germany, Switzerland, and France, he joined the smallpox clinic at the Berlin Charité hospital to rise to become full professor of Neurology and Psychiatry (Nervenkraknheiten) in 1865, where he trained a number of well-known physicians, including Arnold Pick and Carl Wernicke. His achievements are numerous and include the first descriptions of agoraphobia; the first description of periodic paralysis; the report of a relationship between tabes dorsalis and general paralysis of the insane, prefiguring the syphilis connection; work on pseudosclerosis; and (in 1875) the first description of the deep tendon reflex. In 1887, two years after Ludwig Edinger's description in embryos, he described the accessory nucleus of the 3rd nerve which bears his name. His picture is that of a well-groomed, bearded aristocratic man with a bow tie (Figure 1).

Figure 1 Portrait of Karl Friedrich Otto Westphal (1833–1890). *Source*: From Ref. 22.

Dr. Westphal died in 1890 and is not frequently credited for his report on narcolepsy, which has been linked to the possible forensic implications of sleep attacks (6).

Jean Baptiste Edouard Gélineau had quite a different career, outside of the medical establishment. Born in 1828 close to Bordeaux in the south of France (Blaye, Gascony), he was educated as a navy physician in Rochefort, and practiced on ships, studying tropical disorders in his frequent and long travels to the Indian Ocean. He spent the war as a surgeon-major and was decorated for his services (3). With his large lamb chop beard (Figure 2), it is easy to imagine him with the flamboyant and proud character of people born in the country of Cyrano de Bergerac and of the three Musketeers. Not only was Dr. Gélineau a prolific writer of medical articles and monographs, he also had a great deal of business acumen. Dr. Gélineau was known for his arsenic-bromide tablets to calm neurosis and epilepsy, was involved in coordinating a medical insurance system for older physicians and founded a successful society of health spas and mineral waters. In 1878, he moved to Paris, to rapidly establish a successful private practice, a position he only left in 1900 to retire as a wine grower, owner of the castle of Saint-Luce-La-Tour and seller of Bordeaux wines (probably thanks to the success of his tablets). Dr. Gélineau's publications are eclectic and cover literature, history of his native town, commercial ventures and medical studies. His medical work includes observations on tropical diseases, postpartum psychosis, neurosis, angina pectoris, phobias, deafness, and epilepsy. He is credited for coining the term "narcolepsy" in the attached translated 1880 report, and for forcefully defending it as a unique disease entity distinct from epilepsy. Interestingly, Dr. Gélineau also published a monograph in 1880 on agoraphobia (7), himself citing Wesphal's work on

Figure 2 Portrait and signature of Jean Baptiste Gélineau. *Source*: From Ref. 7.

the topic ("agoraphobie des Allemands"). This indicates knowledge of the work of the German physician prior to his 1880 article or discovered just after his Gazette des Hôpitaux publication. In 1881, Dr. Gélineau also wrote a more detailed account on fourteen narcolepsy cases in a monograph "De la narcolepsie" (8), still not citing Westphal's 1878 narcolepsy report. A careful review of the cases reported in the monograph, however, suggests that most if not all (except the original 1880 case) are not genuine narcolepsy-cataplexy. Whether or not Dr. Gélineau spoke German, and whether the two physicians ever met or corresponded is unknown but not impossible.

IV. Further Comments on Westphal's and Gélineau's Descriptions of Narcolepsy

There is no doubt that both Westphal's and Gélineau's cases have genuine narcolepsy with cataplexy. Both physicians report on the presence of sleepiness and of strange episodes of atonia triggered by emotions, which we now call cataplexy. In both cases, onset was somewhat late in life, 34–36 years old and abrupt, following what could be considered a psychological insult. Earlier reports of narcolepsy have been attributed to Willis (1672, in "De anima brutorum"), Schindler (1829), Bright (1836), Graves (1851), Caffé (1862), and Fischer (1878) but described in fact cases of either isolated severe, overwhelming (narcolepsy-like) sleepiness or atypical/imprecisely described (cataplexy-like) "fits" (9–11). A missing aspect in these reports is the lack of description of automatic behavior, abnormal dreaming and sleep paralysis, which are however neither mandatory nor specific for narcolepsy. Hypnagnogic hallucinations in particular had been described earlier by Alfred Maury (12), and sleep paralysis by Binns in 1842 and by Mitchell in 1876 (13,14), but were not reported in either case herein. Gelineau's and Westphal's reports are remarkable by their diversity and, in both cases, by the certainty of the two authors reporting on a new disease entity [later authors erroneously equated "narcolepsy" with every condition associated with severe daytime sleepiness (15)]. The descriptions are tainted by their schooling and influenced by their time. Nonetheless, nothing better would be written for many years thereafter and it could be argued that the next major discovery was the documented association of narcolepsy with REM sleep onset by Vogel in 1960 (16).

In Wesphal's report, the description of the case is focused on muscle weakness episodes with persistence of consciousness, and in the discussion (translation abbreviated), the author agonized on whether these episodes do or do not represent genuine epilepsy to summarize wisely that it is impossible to conclude for or against this hypothesis. Westphal pointed out correctly the presence of subtle "positive" motor phenomena during cataplexy consisting of "small sporadic nostril contractions" and "slight twitching movements in the face . . . as were movements of the jaw." The precise observation has been confirmed by electrophysiological recordings (17). Emotional triggers are also noted but are not very well described ("mental stimulation of seeing two boys fighting in the street"; "any type of excitation"). Laughter and joking, for example, are not reported as triggers. It is in this context to note that Oppenheim, in his 1902 article on "Lachschlag" (syncope with laughing), while discussing the differential diagnosis of spells associated with laughing, did not mention narcolepsy (18).

Sleep attacks are noted to occur "especially if not engaged in some physical activity, but is sitting quietly, talking or reading" but also "while standing" and "while walking in the street." Sleep attacks while engaged in physical activity are indeed typical, although not specific, for narcolepsy. A relationship and an association of the muscle weakness episodes with sleepiness is emphasized by Westphal, and considered as an extension of the muscle weakness episodes ("at times, however, these attacks do cause the patient to fall asleep"). The German author did not differentiate completely sleep attacks from cataplectic episodes, an ambiguity which may have reflected the simultaneous co-occurrence of both symptoms in his patient (as can occasionally be observed in narcoleptics). This ambiguity may have also reflected, however, Westphal's uncertainty about the true nature of the sleep attacks. It is of interest to note in fact that in Oppenheim's "Lehrbuch der Nervenkrankheiten," the most important German Textbook of Neurology at the beginning of the 19th Century, such episodes were considered to represent episodes of "psychic immobility" with muscle weakness, rather than "true" sleep attacks (19). Insomnia and the absence of any response to potassium bromate were also noted by Westphal in his report.

Further discussion of Westphal's cases, not translated in this report, also attest to the rise of "pre-psychoanalytic" ideas, already evident in Westphal's prior studies on "sexual inversion" and homosexuality (20). Detailed reference and discussion of the case of Van Zastrow, a famous criminal pedophile evaluated by the author in prison, is made. Contrary to what was generally believed in his time, the author was surprised not to find the criminal epileptic (epilepsy was frequently considered at the time to be a sign of "mental degeneration"), but rather an excessively sleepy person who frequently fell asleep in public (this symptom was severe enough that people were laughing about it). A relationship between his sleepiness and his alleged frequent masturbations, repressed homosexuality and an associated shame is suggested. Whether Mr. Van Zastrow had sleep apnea or Klein Levin syndrome is impossible to reconstitute, but narcolepsy is unlikely.

Gélineau's report is somewhat complementary to Westphal's. Its style is more descriptive, "story telling." A potential head trauma two years prior to onset is reported as a possible contributing factor. Whereas Westphal was interested in both the loss of muscle tone and the sleep attacks (as reflected by the title of his communication), Gélineau was more fascinated by sleep attacks during active tasks such as eating and by the existence of refreshing, short naps. Cataplexy is confused with sleep attacks, but its triggers are very well described, that is, playing cards (and having a good hand), smiling at someone poorly dressed in the street, being surprised by a sudden danger, and anticipating the pleasure of a good play in the theater. Most telling is the story of our patient going to the zoo of the Jardin des Plantes and "falling asleep" in front of the monkey's cage when everyone was laughing around him. The patient had up to 200 episodes per day.

A second article follows the initial report where Gélineau excludes potential differential diagnoses including vertigo, epilepsy, agoraphobia, anxiety, meningitis, and sleeping sickness, and concludes that narcolepsy is a unique disease entity. As mentioned above, Gélineau also wrote a monograph reporting on 13 additional cases, none of whom is likely to have genuine narcolepsy. Gélineau described how decreased brain tissue oxygenation and metabolism in the pons, the "site of emotional regulation and dreams" could occur in selected predisposed patients or was caused, in two patients,

by too much sex ("Venus' pleasures"). Decreased oxygenation would be precipitated by emotions, considered as consuming too much oxygen and energy. Gélineau also reports on numerous therapeutic attempts. Therapies aimed at relieving a potential vasomotor abnormality, including picrotoxin and amyl nitrite to induce vasodilation were tried without success. Further trials with apomorphine had no efficacy. Interestingly, he tried to give strychnine, which is now known to block post-synaptic glycinergic transmission, in particular at the spinal motor neuron, where it could antagonize REM sleep-induced atonia, but obtained only a transitory effect. Dr. Gélineau finally recommended to treat the narcoleptic sleepiness with caffeine [as originally suggested by Willis in 1672 (21)], despite the fact it was of little benefit in his only genuine case. A more potent treatment (ephedrine sulfate) than caffeine was suggested by Janota and Daniels about 50 years later (21).

Gélineau considered, in his monograph, that the sleep of narcoleptic patients was deep and devoid of dreams, which suggests, as stressed below, that the 13 other cases were probably not narcoleptic. Importantly however, he introduced the notion still valid today of a duality in narcolepsy, that of sleepiness associated with falls (also called astasia).

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The English Translations:
The Original Reports on Narcolepy and Cataplexy by Gélineau and Westphal

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"ON NARCOLEPSY"
By Dr. Gélineau

I.

I am proposing the name narcolepsy (from the Greek "narcosis," drowsiness, and "lambanein," to seize, to take) for a rare neurosis, or at least one that has been little known until now, characterized by a sudden, brief, urgent need to sleep, which recurs at varyingly-spaced, close intervals. This name calls to mind narcolepsy's twofold analogy with drowsiness and catalepsy.

Initially, I believed that the case I had observed (reported below) was the only known instance; however, in Dr. Delasiauve's *Journal de medicine mentale*, nos. 8 and 9, vol. II, 1862, I have just read that Dr. Caffe published an initial case of this sleep neurosis in his *Journal des connaissances medicales pratiques* (August 20, 1862). I am pleased to report this case here, as undeniable proof of its existence.

CASE I. "For more than a year," states Dr. Caffe, "I observed an employee of the Grand Cercle, 16 Boulevard Montmartre, who, because of an irresistible and incessant propensity to sleep, was forced to resign his position. This forty-seven year old man was tall and strong, married, and had always lived soberly. He had no history of illness, and the first external sign was heaviness and half-closure of the eyelids. This drowsiness, which varied in severity depending on circumstances, had affected him for more than four years, coming on while he was standing, sitting, lying down, or while walking. If he woke up, he would fall back to sleep immediately. Even the most pressing hunger did little to divert these effects; his face was somewhat pale and puffy; attitude detached; stupor, mental sluggishness; persistent stoutness; effect on overall health.

Various treatments were unsuccessful, and a stay at the spa at Brides served only to improve his condition, but not result in complete recovery.

Later, after a terrifying emotional experience and illicit excesses (abuse of coitus, masturbation, and alcoholic beverages), he suffered hallucination and meningitic delirium, for which he was intensively treated by Dr. Semelaigne."

CASE II (my own observation). Mr. G., age thirty-eight, a barrel seller with a nervous, volatile temperament, came to my clinic on February 15, 1879.

He had not experienced convulsions in his youth, nor syphilis at a later age. He has two children, the elder of whom, age thirteen, always accompanies him, and the second of whom is only a few months old. G.'s father was nervous, but was free from illness; his mother died of cancer, and his brother of a stomach ulcer. He

drinks moderately. Five years ago, he suffered acute rheumatism in the joints and Herpes tonsurans at the same time.

Three years ago, during a heated argument, he received a violent blow of the fist from the other party, to which he responded by striking his opponent with a drill, after which he was physically apprehended by a policeman and imprisoned; it was a deeply distressing incident.

Finally, a short time later, a log fell on his head, although it did not cause any great pain; and I find no sensitivity at that spot nor any depression worthy of note.

For a long time, this individual experienced no consequential phenomena. Only in the past two years, when laughing out loud or when anticipating a good business deal in his profession, he would feel weakness in his legs, which would buckle under him. Later, when playing cards, if he was dealt a good hand he would freeze, unable to move his arms. His head would nod forward and he would fall asleep. He would wake up a minute later. Soon, the slightest emotion—the sight of his barrels, for example—would be enough to bring on sleep, and since then, this urgent need to sleep has bothered him constantly. When he eats, his meal is interrupted four or five times by the need to rest. His eyelids droop, his hands drop the fork, knife, or glass. He has trouble finishing a sentence, falls asleep. Rubbing his eyes to ward off this sensation while seated is of no avail. His hands fall inert, he is overcome, bends forward, and falls asleep. If he is standing in the street, when this need comes over him, he wavers, stumbles like a drunk, hears people accuse him of drinking and make fun of him. He cannot answer them. Their taunting overwhelms him all the more, and he collapses, instinctively avoiding passing carriages or horses by a final effort. When several people then form a circle around him which always happens in Paris, he hears them or perceives them offering sympathy, and their amiability paralyzes him, affecting him even more and preventing him from getting up.

If he experiences a deep emotion, whether painful or joyous, the need to sleep is even more urgent and sudden. Thus, for example, if he is closing a good business deal, if he sees a friend, if he speaks with a stranger for the first time, or if he receives a good hand while playing cards, he collapses and falls asleep. If he goes to the Jardin des Plantes, near the Monkey House, the place where curiosity-seekers, children's nannies, soldiers, and hecklers usually congregate, he falls asleep seeing this whole laughing crowd around him. A bolting horse, a carriage about to cross his path, or the sight of a person grotesquely dressed who causes him to smile is all he needs to suffer an attack.

At the theater, he falls asleep at the mere thought of the pleasure he is going to experience. He falls asleep again when sitting in his seat, and his son has to shake him and pinch him to pull him out of it. Once the actors come on stage, however, the need disappears; he follows the play with great interest, not collapsing for a single instant, unless a poignant act arouses too great an emotion in him.

Bad weather, particularly the approach of a storm, increases the frequency of these sleep attacks; he has experienced up to two hundred per day.

The only way to pull him out of these attacks is to shake him strongly, or to pinch him. When he becomes violently angry, he sleeps less, but longer and deeper. When he wakes up, he walks straight and firmly, until a new sleep attack comes over him a quarter of an hour later.

I will always remember the way he entered my clinic. He was guided and supported by his son, who held him by the arm. No sooner had he passed through the door of my office and turned his eyes toward me, than, frozen, his gaze glazed over, his eyelids drooped, he staggered, stumbled, and fell asleep, onto a chair; his son spoke to him and shook him hard, after which he began to speak to me.

During his sleep, his pulse, which ranges from 66 to 68 ordinarily, immediately drops to 38 to 60. His pupils, which are highly contracted when awake, are slightly less so when he is asleep. His pupils contract once again when they are raised and brought near the light. The attacks last one to five minutes.

In addition, nothing in him gives evidence of a state of illness; he is calm, at ease. He eats well and his night-time sleep is excellent, waking only once. He has coffee once a day and is not constipated. His sexual desires have diminished considerably. I should repeat that he has just had a child; he says, however, that the child was conceived in a moment when the illness came over him.

A member of the mutual aid society, his card bears the diagnosis *morbus sacer*. He has been treated at his home and at Salpetriere. When he was going there, he fell asleep several times at the door of the hospital, then at the door of the room, and finally, for the third time, confronting the doctor whom he was there to consult. They recommended potassium bromide, subcutaneous injections, hydrotherapy, electricity, and finally, they cauterized the nape of his neck, but, he says, none of this brought any improvement.

When asked to explain his disease and its onset as best he could, he said that he never feels any pain when he is overcome. He merely feels a deep heaviness, an intracranial emptiness, a sort of whirlwind spinning around inside his head, and a heavy weight on his forehead and in back of his eyes. His thoughts dim and fade; his eyelids close half way. He continues to hear, and he is conscious. Finally, his eyelids close completely, and he sleeps. All of this occurs very quickly, so that the normal physiological sleep phase which occurs in progressive periods of five, ten, and twenty minutes, lasts at most a few seconds for him.

If one has him close his eyes and asks him to speak and walk, as is done in cases of ataxia, his voice fades out, he falls asleep and collapses, but without disordered movements. If he enters a dark place, such as a cellar, he also has increased tendency to fall asleep. When he descends a steep street, he has difficulty remaining standing; also, when he pushes a wheelbarrow, with a small cart hitched to him from behind, he pulls it along easily behind him by means of a harness, and he does not fall asleep, probably because his will is more intense at that particular moment.

During his morbid sleep, he never releases any urine or fecal matter. At my office, he has on occasion spoken for a half hour without falling asleep.

His memory is not affected in the least. He is aware of the status of his business, and he is actively involved in taking care of it, but he is always accompanied, because he cannot go out alone without risk of danger. When he works alone, he has fewer attacks than when he is with someone; this is because he enjoys talking, becomes animated and falls asleep.

The intermittent appearance of this illness, its frequency, its lack of resulting injury would place it in the category of a neurosis. The question arises, however, as to whether it should be included under a type already known, or whether it deserves

a place apart in this group that is so large and already so numerous? That is what we shall examine.

First, is this a form of *epilepsy*? I do not think so . . . He does not experience either tonic convulsions or clonic movements. He feels when he is pinched. He is always conscious of what is happening around him. When one shakes him, one can rouse him from his sleep. He does not stammer when he wakes up, and he recovers his intellectual faculties, his senses, and his motility immediately. Moreover, far from overwhelming him, this rest seems to be necessary for him, and appears to give him strength. Finally, his recall is perfect. In addition, potassium bromide, that touchstone of epileptic seizures and epilepsy, has had no positive effect on him. Besides, what epileptic, after one or two hundred spells of dizziness and falls per day, would keep his intelligence and memory intact after two years?

Dr. Semelaigne, however, sought to link his subject's illness to epilepsy . . . (remainder of paragraph deleted).

We reproduce our colleague's opinions in full, but they are not at all convincing. Here is a man who has had continual falls and dizziness for four years, and has never had a full, typical epileptic seizure. He falls, and his drowsiness ceases after the attack; he falls and the *ictus* never causes him to fall stiff, with resultant injuries of the type so common among epileptics. He falls and immediately recovers his wits, his intelligence. Ah! This is because his fall is similar to that of a drunken person or a sleeping child. It is a collapse caused and *preceded* by drowsiness, whereas in the epileptic seizure, sleep *comes after* the fall. Let us add, finally, that Dr. Semelaigne does not mention the one thing that, for us, constitutes the *criterion* of epilepsy from its mildest to its most severe manifestations: the loss of memory, of recollection of what just happened. A subject who remembers and is conscious of what is happening and what happened after an attack of dizziness, an absence, a fall, is not an epileptic.

II.

Can one confuse the affliction from which G. suffers with kenophobia (from the Greek "kenon," the void; "phobeo," I fear), or the fear of open spaces, to use Mr. Legrand du Saulle's term, or agoraphobia, as the Germans put it? Not anymore. Clearly, when crossing a fairly wide street, a square, he is frightened, upset, hesitant. But it is less the view of the open space which affects and frightens him than the fear of being surprised by a carriage, a wagon, or horses. When emotion stops him in his tracks is the moment that sleep overcomes him, and freezes him in place. Also, a person suffering from kenophobia does not fall asleep . . .

One cannot confuse this affliction with vertigo accompanied by syncope, falling, and the loss of consciousness . . . Finally, what a difference between G., sleeping peacefully, blissfully, his face colored, in comparison to the appearance of a livid, frozen man covered with cold sweat and as pale as death, plunged into syncope!

Dr. Casse had attributed this condition of illness to a *serous and passive congestion of the meninges and of the brain.* I assert that this anatomical injury is difficult to reconcile with an intermittent symptom such as sleep that appears and disappears several times a day . . . whereas the idea of a spasm makes it quite easy to explain.

Can this affliction be linked to various degrees of morbid sleep which have been somewhat forgotten in our day, but which the ancients were careful to distinguish in theirs: cataphora, sopor, stupor, coma, carus, and lethargy? The form, duration, and idiotic insensitivity which characterize these last three types make the comparison impossible from the outset.

Perhaps one could associate it with cataphora, and, if one were to consider only the meaning of the Greek words ("kata," down; "pherein," to carry), one would actually believe in a certain analogy between these two types of sleep. But in cataphora, sleep, which is easily interrupted as in the case of G., starts again as soon as one stops speaking to the patient. The sleep is continuous, of a certain duration, and does not include long intervals in which the subject thinks, acts, and works. Finally, cataphora would not be prolonged for years without ending in death or recovery.

As for *sopor* or drowsiness, an intermediate stage between cataphora and coma, the difference is even more marked. The patient, lying on his back, sleeps even more soundly, and cannot be awakened without great effort, and exhibits clearly defined cerebral symptoms, cephalgia, dizziness, loss of memory, akinesia. However, our patient has no symptoms indicating a cerebral illness . . . and ultimately has more waking hours than sleeping.

Confusion with what the English call "sleeping dropsy," which Dr. Nicolas calls "somnosis" and Dr. Dangaix calls "hypnosis," is impossible . . . Dr. Nicolas recently (reports from the Academy of Sciences, issue of May 10, 1880) outlined the progressive and fatal evolution of sleeping sickness from initial drowsiness to death. Sleeping sickness, he says, begins with drowsiness that is completely indistinguishable from normal drowsiness, and its progression is marked by increments that start with deep sleep, followed by longer and longer periods of sleep, until finally the patient does not wake up again. I might add that, being familiar with the work of my friend, Dr. Nicolas, I invited him to examine this patient with me, and that, as a qualified judge of such matters, he immediately rejected any idea of an analogy between these two afflictions.

I had thought of associating the illness with the particular form of nervous condition that was so well described by Morel under the name *emotive delirium*. I found this idea attractive for a short while. In fact, there is no disputing that G. does have a very obvious degree of emotionality, and that this emotionality provokes the attacks . . . Although it is true that the two illnesses appear in response to the slightest of causes, and even the most bizarre, it all adds up to just one effect for G., namely sleep, whereas the scene is quite complex and varied in emotive delirium, accompanied by agitation, anxiety, palpitations, and clouding of the senses, rapid pulse, exaggeration of ideas, and finally automatism. There is nothing of this sort with G. *He falls asleep without suffering*; a subject suffering from emotive delirium . . . *suffers without falling asleep.*

We also do not believe that it can be considered incipient *ataxia* for short periods, because there are no flashes or jerky movements.

The reduction of strength, motility, and the will in G. also made me think of the *neurasthenic* form of *spinal irritation*. However . . . all the facts are in contrast to cases of neurasthenia.

Therefore, I feel justified in designating *narcolepsy* as a specific neurosis, little known until now, and it is good to draw the attention of observers to it.

Let us remember what happened with agoraphobia, which was long confused with vertigo. Once identified, many practitioners in every country throughout the world began to recognize it immediately. Perhaps the same will be true for narcolepsy, which we consider a specific neurosis, characterized by the twofold criterion of drowsiness and falling or astasia . . .

A few words of explanation regarding the cause . . . will help us, I believe, explain the pathogenesis of this neurosis.

Probably, through a special idiosyncrasy, the amount of oxygen accumulated in the nerve centers is in too short supply there, or the oxygen is exhausted too rapidly under the influence of emotions that are too frequent or too strong. The cerebral wear for G. is perhaps greater than in other people, the arterial capillaries too few or too narrow. Perhaps he experiences too rapid an elimination of the regressive products, particularly phosphates.

Whatever the case may be . . . on each occasion, he is neuroparalyzed or, to put it better, neurolyzed, which results in the frequent need to sleep, sleep being the greatest and most powerful restorer of the weakened organism. This opinion is shared by Dr. Delasiauve who, early in his journal, wrote that, "exposed to rapid losses, the nervous system needs to be reimmersed in immobility and rest."

Given this explanation, borrowed from physiology, if we try to determine the exact anatomical location of this neurosis, I believe that, supported by the authority of Dr. Vulpian, we can place it in the annular protuberance. "The annular protuberance," says Dr. Vulpian (1), "must be considered the center of association for emotional movements: whether the excitement comes from the brain or from outside . . . in great emotional expressions, in dreams and in crying, the protuberance plays the most significant role . . . The result is, on the one hand, a momentary paralysis of the cerebrospinal axis, a suspension of nervosity, resulting in astasia and falling and, on the other hand, momentary anemia which, in turn, causes sleep. These two results that constitute narcolepsy are immediate because, in G., there is some sort of shattering of the annular protuberance and cerebral stun.

To complete this observation, I must say something about the treatment that I employed.

Initially . . . I used picrotoxin . . . and I added various bromides to reduce irritability and the reflex action of the cerebrospinal axis.

I must admit that I did not achieve any positive results by using this medication. On the contrary, my patient lost strength and had an increased tendency to sleep. I abandoned that approach.

Along the same lines, I advised that he inhale amyl nitrite vapors poured onto a handkerchief as soon as the narcoleptic attack began . . . We did not overlook the fact that G.'s pulse fell even further, clearly causing an intracranial void, a whirlwind blowing in his head. The use of this medication thus seemed to be indicated . . . But its use did not prevent the attacks, and we then abandoned it, convinced that cerebral anemia played no role in the neurosis at hand.

Then I used subcutaneous injections of apomorphine, which are extolled in Germany . . . without obtaining any positive results.

Then, I decided to turn the symptoms into a medicine, that is, directly fighting the drowsiness. I placed a seton directly on the nape of the neck, which I maintained, and I prescribed grains of caffeine and caffeine valerianate. He improved slightly, but, being

eager for more pronounced results, I was perhaps mistaken in abandoning this medication to consider another idea.

I used strychnine arsenate in progressive doses, and I did not stop until the patient felt tremors in his limbs. I hoped that using this power agent, I would increase the general tone of the economy, fighting the collapses and constant neurolytic exhaustion. At the same time, I had him take phosphates, very tonic food, and warm showers that were revulsant on the spinal column. I even used hypodermic injections of curare. In sum, I did my best to treat the patient aggressively. Nevertheless, I must admit in all humility that by using these methods I barely managed to obtain a few hours of rest and constant work without sleep in the morning and evening. As we both acknowledged that these successes were not in keeping with our mutual efforts, we lost contact, leaving to time and to nature the care of healing or improving this painful neurosis.

Is the ineffectiveness of these remedies one of the characteristics of this neurosis? . . . .

It is clear from what we have said above that the treatment of narcolepsy is entirely open to study. This is one more point of similarity that it shares with the other neuroses, which are so often the stumbling block of our therapeutic means. Whatever the case may be, I am glad to have been able to present this initial study to my colleagues. I am sure that it will result in further studies, for I have already received from a doctor in Lyon all the elements of a third observation of narcolepsy, which I propose to publish somewhat later.

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"TWO MEDICAL CASES"Presented at the Berlin Medical and Psychological Society
By Prof. C. Westphal
I. Larvate epileptic attacks many years before the outbreak of a paralytic mental disorder. (pages 622–631).
II. Peculiar attacks associated with falling asleep. (pages 631–635).

II.

Mr. Ehlert, a bookbinder, was admitted to Charité for the first time on July 18, 1871. He has been admitted a few times since then, and is there now. He is 36, and is reported always to have been healthy. Approximately three months before his first admittance, he became ill, he says, as the result of a fit of anger. He had lost his job because of quarreling. After having a few drinks of schnapps (he is reputedly not a drinker), he went home, where he was scolded by his wife. Soon thereafter, he had a brief "fit" (1—1 1/2 minutes), characterized by a loss of speech, or at least an inability to express words clearly. His whole body was trembling (the patient called it "agitation"), so that he had to sit down (he reported that he had an "involuntary compulsion to sit down"). This "agitation" is said to have continued throughout the entire evening. He slept well that night. He says that he felt completely fine the next day, but a similar

condition (in which he lost his capacity to speak and experienced trembling) occurred thereafter at the least mental stimulation, for example, once when he saw two boys fighting in the street and had, in his mind, taken sides with one of them. Headaches and other complaints never occurred in these instances. Thereafter he was employed in a workshop, which was heated even on hot days. He cites these circumstances as the reason for the increased frequency of the attacks. Approximately 10 weeks before his admittance, the attacks changed so that his teeth chattered, speaking was difficult and, if he had anything in his hands, he would have to lay it aside, because he did not have the strength to continue holding it. During these attacks, he was unable to raise his arms. If the attack came upon him while walking or standing, he had to find some means of support, although a cane was sufficient for the purpose. These attacks varied in duration, depending on whether he had exerted himself beforehand. *He did not lose consciousness during these attacks.* He understood everything when spoken to; he was simply unable to respond coherently or fluently. He always had to close his eyes when doing so.

According to the patient, his mother, who had been struck in the head by a falling brick earlier, also suffers from similar attacks. Specifically, her attacks occur while she is sitting quietly, sewing, eating, or while drinking coffee from her saucer, for example. When asked, he expressly stated that these occurrences in his 61-year-old mother were not caused by any type of senility, and that she had been troubled by such attacks frequently earlier on.

I have had the opportunity to observe the attacks in the patient himself on repeated occasions. He had one of these attacks while I was engaged in conversation with him. While he was still speaking, one could see that a certain change had occurred in his facial coloration, his upper eyelids lowered gradually like those of a person falling asleep (during which the eyes roll upward). Then they opened again once or twice, seemingly with great effort, until they finally shut completely, whereupon the patient stopped speaking after murmuring something incomprehensible. His head sank down to his chest, and his brow seemed forcefully knit. Small sporadic nostril contractions were observable, and the patient's appearance was that of a seated person asleep. After a short time (several minutes), the eyebrows relaxed, the patient raised his right arm a few times as if stretching upward, and rubbed his eyes sleepily, like one awakening from slumber. The scene then repeated itself all over again, during which one could observe that, though apparently asleep, the patient hears if one addresses him, since he nods in response to questions directed to him. Afterwards, he also knows everything that was said during the time.

He experiences many such attacks all day long, especially if he is not engaged in some physical activity, but is sitting quietly, talking or reading. However, even when occupied in a physical task he often undergoes these attacks, e.g. while helping wash the dishes. He then sits down on a bench, continues holding the objects that he had in his hand, nods off, and usually returns to his activity a few minutes later. As he says, he has noticed, as corroborated by others, that the attacks certainly usually start at a specific place in a particular situation. For example, from time to time he has to get papers and other objects from the chief attendant's office. Almost always, while standing, he nods off as described above immediately after picking up these objects; he staggers, with his head on his chest and his trunk bent forward like one intoxicated with sleep, from the office out into the corridor. He then proceeds down the corridor,

and after taking a few steps the attack is over. He never drops the objects given to him, but he holds them differently. He does not carry them with outstretched arms, as before, but his arms hang down loose. He does not lose consciousness at all during these attacks. He says that when he enters the office, his spirit becomes uneasy, that he feels a kind of anxiety, and it seems to him as though something had happened to him there before.

The attacks always come on suddenly. When he was a porter, he had such an attack when a man was giving him an order. The man thought that he was drunk, and told a policeman who happened to be there that he wanted him arrested. Meanwhile the attack passed, and the policeman was quite amazed when the patient reasonably explained to him that it was a medical condition. The patient still had time to run after the man, and to ask him for the order again. He further related that once, when he was leaning far forward over the table to get something from the other side, he experienced an attack in that position, and that he stayed in that position until it had passed.

His information about the sensations that he has during these attacks is as follows. His eyes close involuntarily, and he cannot keep them open. If he manages to open them for a moment, he sees a bright light, but cannot make anything out distinctly. At the same time, he loses all strength in his limbs and the ability to speak. He cannot move, and must sit or lean on something. He says that he does not feel tired like someone on the verge of falling asleep. In his mind, it is as though he were thinking of nothing at all, as if his thoughts were wandering completely. He could not provide a more specific description of his mental condition. He says that he does not experience any dizziness. He reports that he hears and understands what is said to him during the attack, but only pays attention to it if it interests him somewhat.

At times, however, these attacks do cause the patient to fall asleep. The falling asleep appears, as it were, to be an extension or increase of the attack. He says that if he can stretch, the attacks do not go to that extreme. During visits, one often finds the patient already asleep, and one can observe him for fairly long periods at a stretch in that condition. The image is exactly that of a person sleeping peacefully in a seated position. By simply calling his name, he can always be awakened, is aware that he had been sleeping, and notes particularly that upon awakening he is immediately lively and alert, not drowsy. He has also experienced this actual falling asleep while walking in the street. Most often, he steps into the gutter or runs into a lamppost or a person, whereby he is suddenly awakened. He has also stayed asleep in the street and a passer-by, tapping him on the shoulder, wakes him saying, "My good man, you're asleep!" Occasionally another attack occurs after he walks about another hundred paces. This falling asleep in the street, says the patient, usually does not happen if he has a specific destination, but occurs more often when he is strolling around quietly and aimlessly.

Aside from what has been described above, the patient also has attacks that he characterizes as more severe. I was witness to one, which he says falls into this category. The patient was brought into the room by an attendant walking behind him. The patient was completely limp, his eyes were closed, and he was staggering like an intoxicated person, and had difficulty in maintaining his balance. Then all support was removed, and the patient stood free, with only a slight swaying motion, but did not fall. During this time, slight twitching movements in the face were observed, as

were movements of the jaw. The eyes were half shut, and the whites of the eyes, which appeared to be rolled up and to the right, remained visible. Respiration was rapid, with sighing. At times it seemed as though the patient was searching for a chair or a seat to hold himself up, but he only made motions with his head that corresponded to such a search, and did not use his eyes. Finally, he was able to reach the edge of a bed, which he then held onto. Toward the end of the attack, he murmured, "Chair," and then said immediately, "Professor, please excuse me while I take a seat," with his eyes still half shut and continued rapid breathing. Although the attack had given the observers the impression that the patient had been unconscious, when asked, he said that he had been fully conscious during the entire attack, and knew exactly which attendant had brought him into the room.

No specific indication of the onset of the attack in this or any form can be determined through observation. The patient himself states quite clearly that any type of excitation, even of the most minimal kind, is very often the trigger for the attacks. He says that they often occur immediately after such excitation.

The patient's intelligence leaves nothing to be desired, and his demeanor is generally calm and reasonable, and no particularly violent outbreaks have ever occurred, as far as we know, although he is easily roused.

Finally, persistent *night-time sleeplessness* must be noted. He says that he spends only a very small portion of the night sleeping, and that the night-time disturbances of other patients are a kind of entertainment for him, rather than making him uncomfortable.

During his first stay at Charité (July 18, 1871 to December 22, 1871), he was treated consistently with potassium bromate, but to no avail.

As is clear from the medical history, the patient attributes the onset of these attacks to a significant emotion. It is also noteworthy that his mother at times falls asleep while performing ordinary chores. However, the patient notes that there is a difference, in that his mother does not lose control of her limbs during the attacks, as he does, but that when she is drinking coffee, for example, the hand bringing the full saucer to her mouth remains in that position, whereas it would be impossible for him to maintain such a position.

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One is faced with a predicament in attempting to attribute a name to the illness described above. It would be a simple matter to call these episodes "epileptoid" attacks, as well, and I cannot object to the term, if one wishes to lengthen the list of very varied conditions commonly called by that name. This does not advance our understanding at all, however, and the peculiarity of the attacks, to which I need not add any further detail given the exhaustive description above, persists nonetheless.

In this instance. . .one cannot deny that if additional observations should uncover a fairly common occurrence of such "sleep attacks," then we are in the presence of a pathological manifestation of the nervous system, which . . . deserves no less consideration than epileptic or epileptoid attacks. It is evident that for the time being nothing less than a disease of the central nervous system can be concluded . . .

3
Historical Aspects of the Treatment for Narcolepsy

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I. Introduction

Treatment that had a significant effect on narcolepsy was not found for many years after this disease was first described in the medical literature by Caffé in 1862. Gélineau, who denominated narcolepsy in 1880 after having tried various drugs available at that time, reported that he could not find any means for healing or improving dramatically the distressing condition of narcolepsy (1).

The basic disorder in narcolepsy is timing of sleep waking. Its main symptoms are excessive daytime sleepiness (EDS), irresistible sleep episodes (ISE), nocturnal sleep disruptions, cataplexy, sleep paralysis, and hypnagogic hallucinations. These symptoms are frequently found in many, but not in every patient of narcolepsy.

In the past 75 years, about 20 drugs were reported to be effective for the treatment of narcolepsy, some of them widely used. However, every pharmacologic treatment available was symptomatic, and had to be maintained for many years, often life long. In addition, some drugs (CNS stimulants) were effective for EDS and ISE, but were not effective for the other symptoms including cataplexy. Some other drugs (antidepressants) were effective for cataplexy and other REM sleep related symptoms, but they were not effective for EDS and ISE. For treating nocturnal sleep disruptions, hypnotic drugs were often used. Therefore, depending upon the variety of symptoms found in narcoleptic patients, a combined use of two or three different drugs was often necessary. Even with the most recently developed drugs, pharmacologic treatment has not been satisfying in many patients. Based on this evidence, the importance of psychosocial counseling and behavioral modification of narcoleptic patients has been repeatedly emphasized in recent years.

II. Pharmacologic Treatment

Pharmacologic treatment has been the fundamental means for managing narcoleptic symptoms. The available therapeutic drugs can be classified into three groups. One group consists of CNS stimulants effective for EDS and ISE. Some drugs belonging to this group were found to be effective earlier then those belonging to the second group, consisting of antidepressant drugs effective for controlling the REM sleep related symptoms of cataplexy, sleep paralysis, and hypnagogic hallucinations. The

last group consists of hypnotic drugs for treating nocturnal sleep disruptions. Historical aspects of development of the drugs belonging to the three groups are described separately below.

A. Treatment for EDS and ISE

Coffee and tea, both of which contain caffeine with CNS stimulating action, have long been used by many people in different countries as favorite drinks for dissipating sleepiness and keeping alert. Many narcoleptic patients must have used these drinks repeatedly in daily life. But the effects of coffee and tea were very mild and insufficient for controlling EDS and ISE in narcoleptic patients. Gélineau in 1880 described the very mild and insufficient effects of caffeine granules for treating EDS in narcoleptic patients (1). About 50 years later, ephedrine was introduced by Doyle and Daniels (1931) for the treatment of narcolepsy, but the effect of ephedrine was also very mild compared with the effect of amphetamine, introduced to the treatment of narcolepsy by Prinzmental and Blooming in 1935 (2). Within about 70 years after their report, several other CNS stimulants were found to be effective for treating the EDS and ISE of narcolepsy. They are methamphetamine, pipradrol, methyphenidate, pemoline, mazindol, selegiline (MAO-B-inhibitor, converted in vivo into amphetamine), and modafinil (3–5). Recently, amphetamine, methamphetamine, methylphenidate, and modafinil have been widely used for the treatment of narcolepsy. In actual treatment, one of these CNS stimulants is administered in two divided doses in the morning and at lunchtime, but it must not be administered after the evening as it may disturb nocturnal sleep. The therapeutic effect of the above described CNS stimulants upon cataplexy was absent or very mild, if ever.

B. Treatment for Cataplexy and Other REM Sleep Related Symptoms

Good therapeutic effects of imipramine, a tricyclic antidepressant, on cataplexy were first reported by Akimoto et al. in 1960 (7). They were all neuropsychiatrists, who were usually engaged in the treatment of narcoleptic patients as well as depressed, psychotic patients. Prior to their study with imipramine in narcoleptic patients, they had assumed that the antidepressant might elevate the activity level of the brain in narcoleptic patients producing favorable effects on narcoleptic symptoms, Particularly on EDS and ISE. Their assumption was favorably based upon analogical inference from the therapeutic effect of the drug improving the mood state and analogical inference from the therapeutic effect of the drug improving the mood state and elevating the activity level of depressed, psychotic patients (imipramine was the only antipressant available at that time). Unexpectedly, Akimoto et al. (1960) found in several narcoleptic patients that imipramine had significantly favorable effects in reducing the episodes of cataplexy, but that the drug had no effect at all for controlling EDS and ISE.

Shortly after the above report on imipramine, Hishikawa et al. (1966) confirmed the favorable effect of imipramine and cataplexy. In addition, they found that both imipramine and desmethylimipramine, an antidepressant, were significantly effective for controlling not only cataplexy but also sleep paralysis and hypnagogic hallucinations, but that the both drugs were not effective for EDS and ISE (3). Hishikawa et al. also found that cataplexy was closely related to the abnormal disposition in narcoleptic

patients showing the REM sleep period frequently at sleep onset (sleep onset REM period), and that narcoleptic patients experienced sleep paralysis and hypnagogic hallucination exclusively in the sleep onset REM period (8,9). In addition, they found that both imipramine and desmethylimpramine had potent suppressing effects upon REM sleep (10). Based on these findings, Hishikawa et al. proposed that the good therapeutic effects of the antidepressants (imipramine, desmethylimipramine) were due to their REM sleep suppressing action (3), or that the drug effects were due to suppressing some of the neural activities for REM sleep (11).

After the above reports on imipramine and desmethylimipramine (both of them tricyclic antipressants), many other antidepressants were developed, and some of them found to be effective not only upon cataplexy but also on other REM sleep related symptoms in narcoleptic patients. Later antidepressants found to be effective for narcoleptic symptoms were tricyclic antidepressant (protriptyline, clomipramine); selective serotonin reuptake inhibitor: SSRI (fluoxetime, fluoxamine, zimelidine); selective noradrenalin reuptake inhibitor: SNRI (viloxazine); and selective serotonin/noradrenalin reuptake inhibitor: SSNRI (venlafaxine) (5,6,12).

All of these drugs were originally development as antidepressants for treating depression, and were later found to be effective for treatment of narcoleptic symptoms. They were commonly effective for cataplexy, but not effective for EDS and ISE. The tricyclic antidepressants commonly have serotonin and noradrenalin reuptake inhibitory action together with anticholinergic action. These tricyclic antidepressants often produce different side effects including atropinic side effects. Compared with these tricyclic antidepressants, later developed SSRI, SNRI and SSNRI had reuptake inhibitory action selective for serotonin and/or noradrenelin, but had no anticholinergic action. From these, SSRI, SNRI, and SSNRI were considered to have no atropinic side effects and much fewer side effects than the tricyclic antidepressants.

Some of the above described antidepressants have been widely used for the treatment of narcolepsy. In actual treatment, one of the antidepressants was usually administered in a single dose at bedtime or in two divided doses in the morning and at lunchtime or at bedtime. For treating narcoleptic patients suffering from cataplexy in addition to EDS and ISE, a combined use of an antidepressant and a CNS stimulant was usually performed (3,5). In recent years, clomipramine or protriptyline were more widely used. For patients with troubling side effects due to tricyclic antidepressants, one of the SSRIs should be used instead of the tricyclic antidepressants. It must be noted that abrupt discontinuation of drugs for treating cataplexy may often lead to a rebound increase of the episode of cataplexy or to a continuous incapacitaing state called "status cataplecticus."

C. Treatment for Disrupted Nocturnal Sleep

Narcoleptic patients often suffer from disrupted nocturnal sleep characterized by frequent, vivid dreams and interrupting awakenings. Muscle twitches and periodic limb movements frequently occur in the nocturnal sleep of narcoleptic patients. In former times, barbiturates were often used for treating nocturual sleep disruption. However, tolerance often developed with prolonged use of barbiturates. Because of this, in recent years benzodiazepines or later-developed hypnotics (zopiclone, zolpidem) were often administered at bedtime. For patients suffering from frequent

muscle twitches and periodic limb movements, clonazepam administered at bedtime was found to be helpful. Brouughton and Mamelak (1979) found in narcoleptic patients that gamma-hydroxybutyrate (GHB), a gamma-aminobutyric acid (GABA) precurser, was effective in consolidating nocturnal sleep and in increasing daytime alertness. GHB was also found to be effective in reducing cataplexy (13). In this study, GHB was orally administered in two or three divided doses at bedtime and once or twice on awakening in the middle of the night. It must be remembered that GHB administered in amounts sufficient to induce sleep often gave rise to unusual activity of high amplitude in the humam EEG (14).

III. Psychosocial Counseling and Behavioral Modification

Many narcoleptic patients first receive exact diagnosis and appropriate treatment 10 years or more after the onset of this disease. This was probably because narcolepsy was not well known to patients or to medical doctors in general. Many narcoleptic patients unable to cope with difficulties due to symptoms of the disease often had serious and deleterious effects on work, education, driving, recreation, and family-life. In addition, the effect of pharmacologic treatment was often insufficient for controlling narcoleptic symptoms. especially EDS and ISE. Because of these, many patients were often frustrated and depressed even while on pharmacologic treatment (15). Based on such evidences, many clinical researchers have emphasized the importance of giving narcoleptic patients psychosocial counseling and instructions for behavioral modification prior to and simultaneously with pharmacologic treatment. These were considered to be of great use for improving social adaptation and QOL of narcoleptic patients (5,6,12). Important aspects of psychosocial counseling and behavioral modification advised in the recent years are briefly introduced below.

A. Psychosocial Counseling

Soon after the diagnosis of narcolepsy, all patients and their families should be made aware of that EDS, ISE, and cataplexy are symptoms of a disease called narcolepsy, and that their frequent nappings are not expression of negative attitude or deteriorated behavior due to laziness. In addition, patients should be informed that pharmacologic treatment is available, and that their symptoms will be significantly ameliorated with treatment. These explanations often produce great consolation in many patients, and would significantly alleviate their mental anguish and depression, since they have often been derided and punished for their frequent failure due to EDS and nappings in school and at work (5,6,12,15).

As occupational counseling for narcoleptic patients, it is important to advise them to avoid monotonous and sedentary tasks or jobs that enhance the occurrence of their sleeping episodes. Jobs that require driving for long-distances of shift work, and any job necessitating continuous attention for many hours should be avoided. By marked contrast, occupations that require a continuous level of physical activity can usually be performed adequately by narcoleptic patients (5,6). This information must be given to patients on pharmacologic treatment as well, since EDS and ISE are often refractory to, or insufficiently controlled by, such treatment.

Another important point is to instruct teachers and employers about the nature of the disease to enable them to make appropriate adjustments to schooling and working conditions of narcoleptic patients, and to permit them to take scheduled intermittent rest or brief episodes of sleep (6). A nap for 10 to 15 minuts is often of great use to clear off EDS and to prevent ISE in the following one or two hours.

B. Behavioral Modification

Instruction for behavioral modification should include sleep hygiene and requirements when driving. In general, narcoleptic patients need to keep regular sleep and waking schedules. This is to improve consolidation of nocturnal sleep. Patients with fragmented nocturnal sleep are advised to have sound nocturnal sleep with aid of a hypnotic drug, if necessary. This is important for reducing daytime sleepiness. In addition, it is also important to advise patients to have scheduled short naps three to four times during the daytime. Naps of 10 to 15 minutes are usually very refreshing for most patients. Recommended napping schedules should include naps in mid-morning, soon after lunch, and mid-afternoon. A regular napping schedule will reduce unscheduled EDS and ISE. When narcoleptic patients are adequately treated, driving may be permitted but it must be restricted to short distances. When necessary to drive long-distances, they must stop every one to two hours for a rest or a nap, if necessary (5,6,12).

IV. Conclusions

When reviewing the history of treatment for narcolepsy, we find significant progress but results are not yet satisfying. The goal of treatment for narcolepsy is to maintain patients free of symptoms and side effects of medication. But this goal has rarely been achieved in clinical practice. Physicians caring for narcoleptic patients often must use clinical judgment with a compromise that fits each patient's needs. Patients and clinical doctors both must wait for further progress in the research of therapeutic means for narcolepsy.

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4
Narcolepsy and Hypersomnia: Immunogenetic Aspects of Narcolepsy—Past, Present, and Future

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I. Introduction

A genetic component for narcolepsy has been consistently reported across all cultures. Since its initial description by Westphal in 1877, familial narcolepsy has been described by several authors (1,2), suggesting the existence of predisposing genetic factors. Nevsimalova-Bruhova and Roth reported in 1972 that 39.1% of 23 cases of idiopathic hypersomnia and 32.9% of 85 cases of narcolepsy had a positive family history of hypersomnia or narcolepsy (3), and suggested a polyfactorial type of inheritance with two or more genes to explain the transmission of narcolepsy. Kessler in 1976 (4) analyzed 130 narcoleptic families with a narcolepsy proband, and calculated the heritability of narcolepsy to be 0.74. Baraitzer and Parkes (5) analyzed 50 families with a narcolepsy proband and reported that 52% had affected first-degree relatives. Finally, Honda analyzed the mode of inheritance in 232 families with a narcolepsy proband and in 76 families with an excessive daytime sleepiness (EDS) proband (6), and calculated that the heritability of narcolepsy was 0.33 and the heritability of both narcolepsy and EDS was 0.62. There were no narcolepsy patients in families with an EDS proband. Honda proposed a two-threshold multifactorial inheritance model with dominant human leucocyte antigen (HLA)-Dw2 inheritance.

The field of immunogenetic studies in narcolepsy was launched by the discovery of a strong HLA association in narcolepsy in 1984 (7,8). Since then however, there has been no proof for the direct involvement of the immune system in the pathophysiology of narcolepsy. The nucleotide sequences of the HLA-DQ and DR genes were found to be normal in narcoleptic patients (9,10). The frequency of HLA DR2 in narcolepsy was initially reported as 100%, but later there were many reports on the presence of non-DR2 narcoleptic patients, especially among the African-American population. HLA DQB1*0602 was later found to be more significantly associated with narcolepsy across all ethnic groups (11).

In animal models of narcolepsy, it was recently discovered that the nucleotide sequences of the hypocretin/orexin receptor genes were impaired, which resulted in the functional loss of hypocretin/orexin transmission (12,13). But, with the exception

of one patient, no significant changes in the nucleotide sequences of the hypocretin genes were detected in human narcolepsy (14). This suggests that human narcolepsy is not caused by single gene mutations in the hypocretin genes.

The genotype HLA DQB1*0602 remains closely associated with hypocretin-deficient narcolepsy, but its functional role in the brain is still unclear. Direct molecular research of postmortem brains from narcoleptic patients may open new vistas for understanding the mechanisms underlying the cause of narcolepsy. Various research efforts are now being undertaken to further unravel the molecular mechanisms of narcolepsy.

II. The Diagnosis of Narcolepsy and HLA DR2/DRB1*1501 Frequency in Japan

In Japan, serological HLA typing of DR2 in narcolepsy patients started in May 1983. It was followed by serological HLA-DR15 typing in 1987. Four-digit DNA based HLA typing was introduced in April 2001. Non-DR2 narcoleptic patients were rarely found until 2001 when two other physicians joined our sleep clinic . It was recorded that 11.4% of the narcolepsy patients were HLA-DR2-negative. After the founding of the Japan Somnology Center in Tokyo in May 2003, 3 new physicians having less clinical experience with hypersomnia joined our group. As shown in Table 1, the frequency of patients with a diagnosis of narcolepsy but without HLA DRB1*1501/DQB1*0602 increased to 34.5% (16 out of 55 new patients). The diagnosis of narcolepsy was always clinical and at the initial interview. Most diagnoses of HLA-negative narcolepsy patients were made by the newly arrived physicians. This high non-DR2 frequency has recently decreased to 10.1%, suggesting that increased clinical experience in young physicians yielded more homogenous patients.

Table 1 Changes in HLA-DR2 Frequency in Narcolepsy: Effect of Physician Experience in Sleep Medicine

		No. of new narcoleptic pts		No. of physicians and yrs of sleep-clinic experience		
HLA typing method	Period	Total no. of pts	non-DR2/DR15 pts	>20yrs	20>yrs>3	3yrs >
DR2	May 1983–Sept. 1987	206	0 (0 %)	1	0	0
DR15	Oct. 1987–1999	289	2 (0.7 %)	2	0	0
DRB1*1501/DQB1* 0602	2001–June 2003	79	9 (11.4%)	2	1	1
DRB1*1501/DQB1* 0602	July 2003–Dec. 2003	55	19 (34.5%)	2	2	3
DRB1*1501/DQB1* 0602	Jan. 2004–June. 2004	27	7 (25.9%)	2	2	3
DRB1*1501/DQB1*0602	July 2004–Dec. 2004	89	9 (10.1%)	2	1	4

Diagnosis of narcolepsy was made clinically at the initial interview ($n = 745$).

Clinical findings used to diagnose narcolepsy in my clinic include: recurrent daytime sleep episodes of short duration (<30 minutes), associated with feelings of being refreshed and at least five episodes of clinically confirmed cataplexy. Furthersupporting findings include frequent episodes of hypnagogic hallucinations and sleep paralysis; a positive response to psychostimulants and tricyclic antidepressants. Clinical course and onset of EDS and cataplexy are similar in most patients. A narcoleptoid personality" (i.e., decreased psychic tension and alertness) is another important clinical feature (6). A weak familial predisposition is common. These diagnostic criteria were artificially and instinctively created in order to better select a homogenous group of narcoleptic patients. It is most important for immunogenetic studies to use a stricter diagnostic criteria and definition of EDS symptoms.

In our Center, EDS and cataplexy are considered as minimum requirements for the diagnosis of narcolepsy. We also distinguish narcolepsy from essential hypersomnia syndrome (EHS). Our criteria for diagnosing clinical narcolepsy are as follows: (*i*) recurrent daytime sleep episodes, which include naps, lapses into sleep and sleep attacks, occurring basically every day over a period of at least 3 months; (*ii*) clinical confirmation of cataplexy in the patient's history. Cataplexy is defined as a sudden bilateral loss of skeletal muscle tone provoked by a strong emotion. Our diagnostic criteria for EHS are: (*i*) recurrent daytime sleep episodes, which include naps, lapses into sleep and sleep attacks of short duration (<1 hour), occurring basically every day over a period of at least 6 months; (*ii*) absence of cataplexy; (*iii*) diagnostic criteria for other sleep disorders with recurrent excessive daytime sleep episodes, e.g., sleep-apnea syndrome.

Surprisingly, we found that none of the more than one thousand EHS patients we have diagnosed over the past 40 years ever developed cataplexy. It is possible that pharmacological treatment and good sleep hygiene prevented the development of cataplexy. It is also possible that most of the EHS patients without HLA DRB1*1501/DQB1*0602 are etiologically different from narcolepsy. Figure 1 reports on the differential prognosis of EDS in narcolepsy versus EHS patients. These differences may suggest that these two groups of chronic hypersomnia have different causes.

III. HLA Study of Japanese Families with Multiple Narcoleptic Patients

Family and HLA typing studies have also been performed in our population (15). We now have 15 families with more than two patients with definite narcolepsy. The pedigrees with HLA haplotypes of 3 of these families are shown in Figure 2. All narcoleptic and EDS patients and their family members shared the common HLA haplotype, DRB1*1501/DQB1*0602. The severity of the symptoms of narcolepsy tended to decrease in the younger generations when compared to the older generations. In the third generation, patients with mild EDS severity and no cataplexy were observed, supporting a multifactorial model of inheritance for sleepiness. Such forms of EDS in the families may be considered as aborted forms of narcolepsy. Interestingly, one family (Family C) had a chromosomal recombination between the HLA DR-DQ and HLA A-B-C genes (16). The haplotype DRB1*1501/DQB1*0602 was transmitted to the

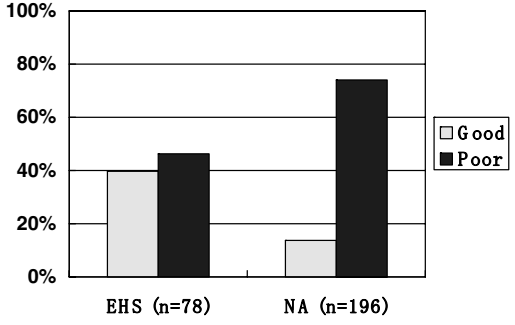
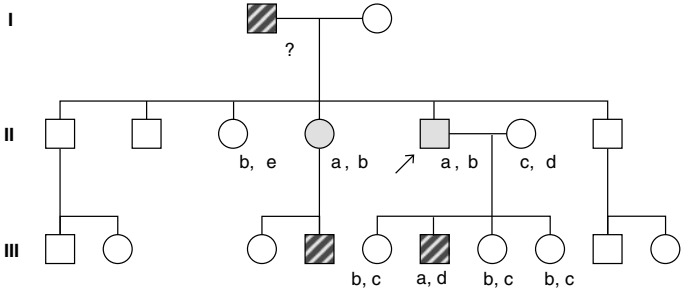


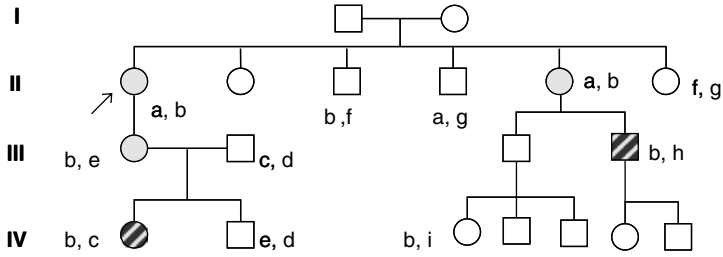
Figure 1 Long-term outcome measures of excessive daytime sleepiness (EDS severity) in narcolepsy and essential hypersomnia syndrome (EHS). Note differences between 196 cases of narcolepsy and 78 cases of EHS for situations without medications over 10 to 40 years. White bars indicate a favorable outcome (marked alleviation of EDS). About 40% of all EHS patients showed absence or rare daytime sleepiness; a similar long-term improvement was observed in only 14% of narcoleptic patients. Black bars indicate poor outcome of EDS after long time course. Note that about 74% of narcolepsy patients still showed frequent EDS in contrast to 46% of EHS. The difference in long-term prognosis indicates etiological difference between narcolepsy and EHS. *Source*: From Ref. 28.



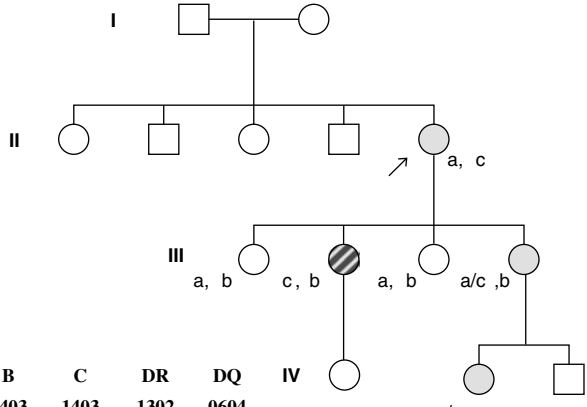
(*a*)

	A	B	C	DR	DQ
a:	0201	5401	0102	1501	0602
b:	0206	5401	0102	0405	0401
c:	1101	1501	0401	0403	0302
d:	0207	4601	0102	0803	0601
e:	3101	4002	0304	1403	0301

Figure 2 Three Japanese multiplex families. Note that all narcoleptic and EDS patients are DRB1*1501/DQB1*0602 positive. Filled boxed indicate narcolepsy and slashed boxes EDS patients. (***a***) Haplotype "a" carries susceptibility to narcolepsy. Note the presence of EDS without cataplexy in the third generation, suggesting decreased severity in descending generations. (***b***) The haplotype "b" carries susceptibility to narcolepsy. A similar decrease of severity was observed in the younger generation. (***c***) The haplotype c carries the susceptibility to narcolepsy. Note the unique translocation of the haplotype DRB1*1501/DQB1*0602 of c with A,B,C of a (a/c) in the second and third generations. The severity of the symptoms of narcolepsy also decrease in the younger generations when compared to the older generations. The patient in the third generation had only mild cataplexy which disappeared later. (*Continued*)



		A	B	C	DR	DQ
	a:	0201	4801	0801	1501	0602
	b:	2603	3501	0303	1501	0602
	c:	2402	0702	0702	0101	0501
	d:	2601	3501	0303	0406	0302
	e:	2402	5401	0102	0405	0401
	f:	0206	5901	0102	0405	0401
	g:	1101	5101	1402	1101	0301
	h:	2602	5401	0102	0405	0401
(*b*)	i:	0207	4601	0102	0901	0303



		A	B	C	DR	DQ
	a:	3303	4403	1403	1302	0604
	b:	2601	4002	0304	0901	0303
	c:	0201	5101	1502	1501	0602
	a/c:	3303	4403	1403	1501	0602
(*c*)	d:	2402	4601	0102	0803	0601

Figure 2 *Continued.*

affected child and grandchild. The recombination breakpoint could be regarded as a boundary for the narcolepsy susceptibility region. Haplotype analyses revealed that the recombination breakpoint was located-50 kb to the telomeric end of the palmitoyl-protein thioesterase-2 gene in the HLA class III region of chromosome 6.