REM Sleep Behavior Disorder: Clinical, Developmental, and Neuroscience Perspectives 16 Years After its Formal Identification in SLEEP

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Key words: REM sleep behavior disorder; parasomnia; REM sleep without atonia; polysomnography; clonazepam; melatonin; neurologic disorders; parkinsonian disorders; developmental biology

“…he was thrusting his sword in all directions, speaking out loud as if he were actually fighting a giant. And the strange thing was that he did not have his eyes open, because he was asleep and dreaming that he was battling the giant… He had stabbed the wine skins so many times, believing that he was stabbing the giant, that the entire room was filled with wine…”

—Miguel de Cervantes, Don Quixote de La Mancha (1605), page 364, Editorial Juventud, S.A., Barcelona, 1995 edition (author’s translation)

INTRODUCTION

REM SLEEP BEHAVIOR DISORDER (RBD) IS A MULTIFACETED PARASOMNIA INVOLVING REM SLEEP AND THE MOTOR SYSTEM IN WHICH THERE IS problematic behavioral release that is usually experienced by the individual as enactment of distinctly altered, unpleasant, and combative dreams.¹² The vigorous and violent “oneiric” behaviors of RBD commonly result in injury, which at times can be severe and even life-threatening. RBD occurs naturally across mammalian species, and there is an experimental animal model of RBD induced by pontine lesions, first described in cats in 1965 by Jouvet and Delorme from Claude Bernard University in Lyons, France.³ RBD is strategically situated within an important and rapidly expanding crossroads of clinical (sleep) medicine and the neurosciences. For example, an area of intense current interest among clinicians and basic scientists concerns the linkage of the extrapyramidal system with brainstem neuronal centers generating the tonic and phasic components of REM sleep. The extrapyramidal and REM sleep systems have strong neuronal connectivities, predisposing them to shared pathologic states, such as the common association of parkinsonian disorders with RBD. The recognition of RBD has also facilitated the identification of other pathologic dissociated states, such as Parasomnia Overlap Disorder, Narcolepsy-RBD, and Status Dissociatus. This is a flourishing era for RBD research, with opportunities emerging for additional scientific disciplines to become involved in the research effort.

RBD in humans was formally identified in the journal SLEEP in 1986, when we reported on a series of five elderly patients.¹ The following year we reported on an expanded series of 10 patients, involving predominantly older men (half of whom had a major neurologic disorder), and we then gave RBD its name as a newly recognized category of parasomnia.² In 1990, RBD was included within the official International Classification of Sleep Disorders, with diagnostic criteria being established.⁴ Various polysomnographic (PSG) and clinical aspects of human RBD had been described in the literature since 1966 by investigators from Europe, Japan and North America, almost exclusively in neurologic settings.¹⁵ Two groups of pioneering investigators should be recognized: Passouant et al. from France identified a dissociated state of REM sleep with tonic muscle activity induced by tricyclic antidepressant medication.⁶ Tachibana et al. from Japan named “stage 1-REM sleep” as a peculiar sleep stage characterized by muscle tone during a REM sleep-like state that emerged during acute psychoses related to alcohol and meprobamate abuse.⁷ However, our 1986 report in SLEEP firmly established that RBD is a distinct parasomnia which occurs during unequivocal REM sleep, and which can be idiopathic or symptomatic of a neurologic disorder. Although there is variable loss of the customary, generalized muscle paralysis of REM sleep, we found that all other major features of REM sleep remain intact in RBD (e.g., REM latency, REM %, number of REM periods, and REM/NREM cycling). PSG monitoring of these patients established that RBD did not emerge from a “stage-1 REM sleep” that was separate from REM sleep, nor did RBD emerge from a poorly defined variant of REM sleep, or from an unknown or “peculiar” stage of sleep, or during “delirious” awakenings from sleep—all of which had been mentioned in the literature. Our 1986 report also called attention to generalized motor dyscontrol across REM and NREM sleep, manifesting as increased muscle tone and/or excessive phasic muscle twitching in REM sleep, along with periodic limb movements and non-periodic limb twitching in NREM sleep. A lengthy prodrome in RBD was also identified; a characteristic dream disturbance was described; and successful treatment with bedtime clonazepam was identified.

In this report, we will summarize the main findings of our 1986 report; describe the animal model of RBD; elaborate on the clinical features of RBD; provide major findings from three large series of patients with RBD; cover the differential diagnoses of RBD; provide an update of the extensive research on RBD by recognized investigators that illustrates the vital interdependence of clinical medicine and basic science;⁸ call attention to a spectrum of dissociated behavioral states, of which RBD is a striking
example; and present some future directions in RBD research.

Summary of “Chronic Behavioral Disorders of Human REM Sleep: A New Category of Parasomnia”

The setting for our 1986 report on RBD was a hospital-based, multi-disciplinary, sleep disorders center, with a broad referral base. During routine clinical work, we identified five patients, 60-72 years old, with similar behavioral disturbances during REM sleep. Our index case referred to his condition as “physically moving dreams” and as “violent moving nightmares.” These patients had been previously misdiagnosed because of their histories of dangerous dream-enacting behaviors. Four patients had diverse neurologic disorders closely associated with RBD. Our initial treatment approach was to use REM-suppressing tricyclic antidepressants, but this was unsuccessful, apart from one patient responding to desipramine. Clonazepam, a potent benzodiazepine agent, was then selected to treat RBD, since three patients also had periodic limb movements (PLMs), and there were published reports on the efficacy of clonazepam in treating PLM disorder (“nocturnal myoclonus”). Our rationale was that if clonazepam was effective in controlling one sleep motor disorder, it might also be effective in controlling another sleep motor disorder. Clonazepam therapy was found to be immediately effective in controlling RBD and its disturbed dreams, raising the question of whether a common neuronal generator exists in REM sleep for both behavior patterns and their dream patterns.

It was also notable that repeated nocturnal violence did not threaten the stability of the four marriages in our report. The spouses realized that their husbands were acting out of character in their sleep, since during the daytime these men were placid, mild-mannered, and without any propensity for irritability or angry outbursts. The spouses remained in bed with their husbands—even though their own sleep was being threatened and disrupted—so as to prevent any injury during sleep. Men with RBD often dreamt that they were fighting to protect their wives from an attacker—only to find out, upon awakening, that they were actually attacking their wives in bed.

Our patients with RBD, prior to diagnosis and treatment, often devised their own “home remedies” to protect themselves during sleep, such as sleeping on a mattress or in sleeping bags on the floor of a room devoid of furniture; tethering themselves to their beds with belts and ropes (Figure 1); sleeping in a padded waterbed; using pillow barricades, or ceiling-to-floor plastic sheets.

Animal Model of RBD: Paradox Lost

The foundation for understanding human RBD resides with the experimental animal model of RBD, which, in turn, is dependent on understanding some of the basic neurophysiology of REM sleep. REM sleep in mammals involves a highly energized state of brain activity, with both tonic (i.e. continuous) and phasic (i.e. intermittent) activation occurring across a spectrum of physiologic parameters. REM sleep has various physiologically derived synonyms, with basic sleep researchers primarily using the following nomenclature: 1) “Active Sleep” on account of the high level of brain activity (comparable to wakefulness), as measured electrophysiologically, and as measured by cerebral blood flow, oxygen consumption and glucose utilization; and 2) “Paradoxical Sleep” due to the paradoxical suppression of skeletal muscle tone despite a highly activated brain state. The generalized skeletal muscle atonia (“REM-atonia”) is a defining feature of REM sleep, along with rapid eye movements (REMs) and an activated EEG. A major share of the high energy available during REM sleep is devoted to the generation and maintenance of REM-atonia. The loss of the paradox of REM sleep in RBD carries major clinical consequences: paradox lost means loss of safe sleep, with dreams being acted out in reality.

In 1965, Jouvet & Delorme reported that experimentally-induced, bilateral, symmetrical, mediodorsal pontine tegmental (electrolytic) lesions in 35 cats (gender not mentioned) resulted in permanent loss of REM-atonia, whereas lesions to other brainstem structures, removal of the cerebellum, or destruction of the upper vestibular nuclei, had no such effect on REM-atonia. These pontine-lesioned cats, approximately two to three weeks after their lesions, also displayed de novo “hallucinatory-type” behaviors during REM sleep that strongly resembled “oneirism,” (i.e., dream enactment). Furthermore, NREM sleep was also perturbed in these cats, with frequent intrusions of ponto-geniculo-occipital (PGO) waves (a hallmark phasic REM sleep phenomenon), along with excessive, simple movements of the paws and vibrissas during NREM sleep. Thus, Jouvet and Delorme emphasized the importance of both the loss of REM-atonia and the enhancement of phasic electrophysiologic and motor activity in NREM sleep in the pathophysiology of their animal model of
RBD. This observation is mirrored in the findings with human RBD.

Jouvet’s group published additional findings on their experimental cat RBD model, which they called the “paradoxical sleep without atonia” preparation.9,10 They found that a highly stereotypic and restricted repertoire of behaviors is spontaneously displayed during REM sleep in an experimental group of six adult, male and female, cats—in the absence of any environmental stimulation or provocation.9 “After the orienting response [to internal stimuli] which begins oneiric behavior, other behavioral sequences follow in a totally unpredictable manner.”9,10 The following behaviors were observed in their “ethological study of spontaneous [post-lesion] behaviors9; 1) “violent and abrupt jerks involving all of the muscles”; 2) “vertical leaps so intense that the animal collides with the ceiling of the cage”; 3) “visual orientation” (following an imaginary object with head and eyes); 4) exploration; 5) stalking, with “almost complete immobility” that is characteristic of wakeful stalking behavior; 6) “predatory aggression” devoid of emotion; 7) aggressive attack, with emotion, against an imaginary enemy; 8) rage, with numerous emotional components; 9) fear, with retracting behavior culminating in a defensive posture; 10) indiscriminate licking and nibbling behavior (self, walls, floor).

A quantitative analysis revealed that attack behavior was the most commonly observed behavior. Nevertheless, in contrast to natural conditions during wakefulness, yowling or crying never accompanied aggressive or rage attacks, nor fear states. Furthermore, feeding, sexual behaviors, rubbing, panting, vomiting and sneezing were never observed during oneiric states. These cats “had never displayed the slightest sign of aggression toward the experimenter during the preoperative period.”9 The following behaviors were observed in their “ethological study of spontaneous [post-lesion] behaviors9; 1) “violent and abrupt jerks involving all of the muscles”; 2) “vertical leaps so intense that the animal collides with the ceiling of the cage”; 3) “visual orientation” (following an imaginary object with head and eyes); 4) exploration; 5) stalking, with “almost complete immobility” that is characteristic of wakeful stalking behavior; 6) “predatory aggression” devoid of emotion; 7) aggressive attack, with emotion, against an imaginary enemy; 8) rage, with numerous emotional components; 9) fear, with retracting behavior culminating in a defensive posture; 10) indiscriminate licking and nibbling behavior (self, walls, floor).

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responsible for tonic motor inhibition, whereas the auditory pres-pulse inhibition of the acoustic startle is not.38

Finally, Morrison's group identified spontaneous (idiopathic or symptomatic) animal RBD—including RBD manifesting as phasic motor over-activation with preservation of REM-atonia—in cats and dogs attending veterinary clinics.39,40 and identified clonazepam as being an effective therapeutic agent.40 Clonazepam was utilized based on our center's success in treating human RBD with this agent. This points out an important human-animal reciprocity, insofar as the animal model of RBD provided a foundation for understanding human RBD, and the successful treatment of human RBD with clonazepam was then utilized in treating spontaneous RBD in household pets brought to veterinary clinics.

Clinical Features of Human REM Sleep Behavior Disorder

RBD has two main clinical forms, 1) acute RBD and 2) chronic RBD. The acute form is usually associated with medication toxicity, drug abuse, drug withdrawal, or withdrawal from alcohol abuse.5,7 In fact, acute RBD with delirium tremens can present as a "RBD Status" disorder.41 To date, three large series on chronic RBD have been reported on 96, 93, and 52 patients.42-44

RBD diagnostic criteria which we have developed consist of:5

1) PSG abnormality during REM sleep: elevated submental electromyographic (EMG) tone and/or excessive phasic submental and/or limb EMG twitching.
2) Documentation of abnormal REM sleep behaviors during PSG studies (prominent limb or truncal jerking; complex, vigorous, or violent behaviors) OR a history of injurious or disruptive sleep behaviors.
3) Absence of EEG epileptiform activity during REM sleep.

The International Classification of Sleep Disorders4 has developed similar criteria, but with problematic minimal diagnostic criteria (B plus C):

A. The patient has a complaint of violent or injurious behavior during sleep.
B. Limb or body movement is associated with dream mentation.
C. At least one of the following occurs:
   1. Harmful or potentially harmful sleep behaviors.
   2. Dreams appear to be "acted out."
   3. Sleep behaviors disrupt sleep continuity.
D. PSG monitoring demonstrates at least one of the following electrophysiologic measures during REM sleep:
   1. Excessive augmentation of chin EMG tone.
   2. Excessive chin or limb phasic EMG twitching, irrespective of chin EMG activity and one or more of the following clinical features during REM sleep:
      a. Excessive limb or body jerking.
      b. Complex, vigorous, or violent behaviors.
      c. Absence of epileptic activity in association with the disorder.
E. The symptoms are not associated with mental disorders, but may be associated with neurologic disorders.

F. Other sleep disorders (e.g., sleep terrors or sleep-walking) can be present but are not the cause of the behavior.

The minimal diagnostic criteria are overly lax, in our opinion, and consist only of two components—neither of which involves PSG monitoring: criteria B plus criteria C. However, given current knowledge of the broad differential diagnosis of dream-enacting behaviors (to be described in a subsequent section) we believe that diagnostic accuracy is compromised by presumptively diagnosing RBD without the benefit of PSG monitoring, which carries adverse clinical and research implications. For example, clonazepam therapy of recurrent dream enactment associated with obstructive sleep apnea (OSA)-induced REM sleep arousals is not only inappropriate therapy for OSA, but may even aggravate OSA if respiratory suppression occurs. Clonazepam therapy of nocturnal seizures with dream enactment may temporarily suppress the dream enactment before a full relapse ensues, since clonazepam does not have sustained anticonvulsant activity for most types of seizures. Clonazepam can also disinhibit nocturnal dissociation in some dream enacting patients with nocturnal dissociative disorders. For research purposes, PSG-based diagnoses are needed to ensure homogeneous patient groupings, since a history of recurrent dream enactment is not pathognomonic of RBD. This point is relevant to a recent report on RBD and post-traumatic stress disorder, in which a PSG was not performed on each patient diagnosed with RBD.45

Major Findings from Three Large Series of Chronic RBD Patients

We will now describe the major findings from a series of 96 consecutively documented cases of RBD from our center,42 and relate them to findings from two other large series of 93 and 52 cases of RBD gathered at the Mayo Clinic43 and from the University of Strasbourg, France,44 with pertinent findings included from other clinical reports on RBD.

1. Male Predominance. This is a striking finding, with 87.5% of our 96 patients, and 87% of the 93 Mayo Clinic patients being male. The Strasbourg series of 52 patients did not contain gender data, but most of the other reported cases of RBD are male. Despite these overwhelming gender data, it is possible that milder forms of RBD exist in women that manifest as subclinical, non-aggressive behaviors that do not call for medical attention. Perhaps there is a large unrecognized group of elderly females who have non-aggressive RBD that does not cause sleep disruption or injury. The role of sex hormones in mediating aggressive and violent behaviors has been reviewed, and may be relevant to the male predominance in RBD.46,47 In addition, gender-specific aging effects on CNS serotonergic (1A receptor) function may contribute to gender differences in behavior, mood, and susceptibility to brain disorders across the adult life span.48 Sex differences in the aging brain have been documented neuroanatomically and by magnetic resonance imaging.49,50

2. Older Male Predominance. Mean age of RBD onset in
our series was 52 years (range, 9-81); in the Mayo Clinic series was 61 years (range 36-84); and in the Strasbourg series was 62 years for an idiopathic group (n=13) and 55 years for a symptomatic group with neurologic disorders (n=39). Most age groups, however, were affected with RBD in these series.

3. **Prodrome.** 25% of patients in our series had a prodrome, observed by a bedpartner, that lasted a mean 22 years (range, 2-48 years) prior to the frank onset of clinical RBD. The prodrome manifested as subclinical behavioral release during (presumed REM) sleep, with persistent sleeptalking, yelling, limb twitching, and gross limb and body jerking—but without complex behaviors. However, childhood histories of sleepwalking and sleep terrors in RBD are quite rare, apart from Parasomnia Overlap Disorder (to be discussed below).

4. **Sleep-related Injury.** This was the presenting complaint in 79% of our series (involving ecchymoses, lacerations, fractures), with injuries to self and bedpartner. In the Mayo Clinic series, 96% of patients injured themselves or assaulted their bedpartner during sleep. The Strasbourg series did not report the chief complaint. Severe reported injuries from RBD include C2 vertebral fracture,\(^51\) and subdural hematomas.\(^52,53\) RBD is a treatable cause of falls in the elderly.\(^54\) The risks of injury from RBD in Intensive Care Unit settings have been discussed, along with management guidelines.\(^55\) Guilleminault et al., in their comments on a group of 48 RBD patients, contrasted the frequent occurrence of self-inflicted injury during sleep with only one instance of a man attacking his wife.\(^56\) However, we reviewed the pertinent literature on RBD in 1995, and by then there were 12 reports on 22 patients with RBD who had repeatedly injured their wives in bed during violent dream enactment, with the risk of lethality being considered especially high in five cases.\(^57\) Therefore, RBD carries a definite, ongoing risk for severe injury to both self and bedpartner.

5. **Dream Enactment.** This was present in 87% of our series, in 93% of the Mayo Clinic series, and in 64% of the Strasbourg series. Dream-enacting behaviors included: talking, laughing, yelling, swearing, gesturing, reaching, grabbing, arm flailing, punching, kicking, sitting, jumping out of bed, crawling, and running. Nevertheless, patients did not act-out their customary dreams, but rather acted out distinctly altered dreams that comprise a core feature of RBD. Figures 2A and 2B are video prints depicting attempted dream enactment during REM sleep in our laboratory.

6. **Altered Dream Process and Content.** Eighty-seven percent of our series reported more vivid, intense, action-filled, and violent dreams coincident with the onset of RBD, and were often experienced as severe nightmares. Fear and anger were usually present during dreams of being chased or attacked by unfamiliar people, animals or insects. The dreamer was rarely the primary aggressor. Abnormal dreaming was reported in 87% of the Mayo Clinic series, with defense against attacks by people and animals being the most common dream scenario, and with a minority of the dreams involving adventure or sports scenarios, or primary aggression by the dreamer. Vivid dreaming during dream enactment was described in 64% of the Strasbourg series. The altered dreaming is typically controlled in tandem with control of the dream-enacting behaviors of RBD with the same therapeutic agent, vis-a-vis. clonazepam. In our series, a subgroup of patients experienced recurrent dreams with presumed vestibular activation, with scenarios involving spinning objects or angular motion with acceleration; another subgroup experienced recurrent atonia suddenly intruding into their dream-enacting episodes, as they would suddenly become stuck in mud, trapped in deep snow, or fall to the ground and not be able to get back up.

7. **Tonic and/or Phasic EMG Abnormalities during REM Sleep.** 100% of our series had excessive loss of REM-atonia and/or distinctly increased phasic EMG activity (irrespective of the amount of behavioral release during REM sleep). Similar findings were reported in 97% of the Mayo Clinic series (with the remaining 3% having abnormal EMG activity during “ambiguous

Figures 2a and 2b—Video prints during REM sleep of an older man with RBD who is shown to be throwing two punches during a 12 punch sequence in which he is dreaming of fighting an attacker.
sleep). In the Strasbourg series, 92% of the idiopathic group had loss of REM-atonia during >90% of their total REM sleep time, whereas in the symptomatic group 51% had preserved REM-atonia during most of their total REM sleep time, with preserved REM-atonia occurring during “simple motor attacks.” Presumably, the symptomatic group had increased phasic EMG activity during REM sleep.

8. Periodic Limb Movements during NREM Sleep. These were present in 61% of our series, and in 47% of the Mayo Clinic series. PLMs in our series were rarely associated with arousals; occurred every 15-30 seconds throughout the entire sleep cycle, and involved the arms and not just the legs. The Mayo Clinic series did not comment on associated arousals, but did specify a minimum PLM hourly index of 20. Furthermore, a 61% prevalence of PLMs (hourly index >10) was found in a study of 36 older male patients with idiopathic RBD by Montplaisir’s group at the University of Montreal. The PLMs in the RBD patients were rarely associated with arousals (Montplaisir, personal communication). In a subsequent study by the same group, cardiac activation during PLMs in 10 idiopathic RBD patients was blunted in comparison to that of 10 RLS patients. Aperodic Movements during NREM Sleep. These were present in 37% of our series, but were not men- tioned in the other two series. In our series, these were infrequently associated with arousals, involved both arms and legs, and could occur throughout the entire sleep cycle.

10. Sleep Architecture is Preserved. Customary cycling among REM and NREM sleep stages was usually preserved, as was the sleep architecture, in all three large series. A shift towards light sleep with an elevated stage 1% can occur in some cases.

11. Elevated Percent of Slow-wave (Stage 3/4) Sleep for Age. In our series, 80% of patients >58 years had >15% slow-wave sleep of total sleep time, which was not associated with prior sleep deprivation, and which was often pronounced. For example, the mean percent of slow-wave sleep for the 52 elevated cases was 26% (range, 15-46%). In the Mayo Clinic series, 33% of patients >58 years had >15% slow-wave sleep of total sleep time. The Strasbourg series did not detect any elevated slow-wave sleep percent, with both the idiopathic (n=13) and symptomatic (n=39) groups having mean SWS percents between 8%-9% (+SEM 1.2-1.7). In contrast, a report from a hospital-based university sleep center in Barcelona, Spain detected increased SWS percent for age in 76% of 25 RBD patients (n=18, male), mean age 58 years; eight patients had idiopathic RBD, and 17 had symptomatic RBD (associated with narcolepsy or various parkinsonian disorders). Furthermore, a pronounced elevation of SWS % in pre-clinical RBD was found in a 70 year-old female with progressive supranuclear palsy who presented with the intriguing contrast of nocturnal somniloquy and daytime inhibition of speech, and who had PSG-documented somniloquy and excessive muscle twitching during REM sleep—and 41% SWS. Thus, another form of NREM sleep dysregulation—increased SWS percent—can occur with RBD, and may be an important component of the RBD syndrome. Our center has explored the distribution of SWS vis-a-vis the distribution of REM sleep in 38 PSG studies of 28 RBD patients (most of whom had elevated SWS%), and concluded that the elevated SWS% most likely derived from CNS dysregulation rather than from a direct energy conservation mechanism, since SWS epochs did not preferentially emerge after REM sleep epochs. Nevertheless, increased amounts of SWS (irrespective of the underlying mechanism) seen in RBD may result in energy conservation as an adaptive epiphenomenon (“a chance benefit”), with the clinical consequence being fully rested upon arising and not fatigued during the day.

12. Other Notable PSG Findings. All PSG and behavioral features of RBD are indistinguishable across subgroups, irrespective of gender, age, presence or absence of a neurological disorder, or duration of RBD. This suggests the presence of a “final common pathway” in RBD that can be accessed by a wide variety of pathologic states. Figures 3-5 depict the major PSG findings in RBD. One finding that merits particular emphasis is that loss of submental (i.e., background) EMG atonia is not necessary for the release of excessive phasic EMG twitching during REM sleep, nor for the expression of
RBD behaviors. Figure 5 illustrates this important point. A study of 17 PSG records from older males with idiopathic RBD found that REM-atonia was preserved in >50% of REM sleep time bins (7.5 seconds) containing bursts of phasic EMG limb twitching.57 Some patients had 99% loss of REM-atonia, whereas other patients had 95% preservation of REM-atonia. Thus, preservation of REM-atonia is often maintained in RBD, despite intense phasic motor activation. RBD behaviors occur within REM sleep, and not during arousals from REM sleep, and are often not accompanied by tachycardia. In line with these clinical observations, a recent study has found that cardiac autonomic sympathetic and parasympathetic activity during REM sleep in human RBD is dampened.66 Sleep disruption from sleep-disordered breathing is uncommon in RBD; when present in RBD, OSA is usually mild. It is possible that RBD may protect against obstructive sleep apnea.67 Nevertheless, clonazepam therapy of RBD may promote OSA in vulnerable patients.68

13. Efficacy of Clonazepam Treatment. In our series, 90% of cases responded completely or substantially to bedtime clonazepam therapy, usually at a dose of 0.5-2.0 mg q hs (at times as high as 4.0 mg). With this treatment, there was rapid control of both problematic sleep behaviors and disturbed dreaming, with efficacy now maintained for 18 years in some patients. The same clonazepam treatment efficacy was reported in the Mayo Clinic series (87%) and in the Strasbourg series (90%). The mechanism of therapeutic action involves suppression of phasic EMG activity (with behavioral control) during REM sleep rather than restoration of REM-atonia.64,69 The long-term efficacy and safety—and lack of significant dose increase—of chronic, nightly clonazepam treatment of RBD, has been documented.54,70 Maximizing the safety of the sleeping environment should also be considered a cornerstone of treatment.

14. Multiple Sleep Latency Testing. Despite the impressive EMG motor activity and repeated behavioral release during sleep, only a small number of RBD patients in our series complained of excessive sleep disruption, daytime fatigue, or excessive daytime sleepiness. Multiple sleep latency testing rarely documents daytime somnolence,64 apart from cases in which RBD is associated with narcolepsy.

15. Associated Disorders. Idiopathic RBD was the initial diagnosis after clinical and PSG evaluations in 42% of our series, in 43% of the Mayo Clinic series, and in 25% of the Strasbourg series. CNS disorders that were causally related to RBD onset were diagnosed in 48% of our series, in 57% of the Mayo Clinic series, and in 75% of the Strasbourg series. One patient in our series developed RBD abruptly, and permanently, after total parathyroidectomy. A psychiatric disorder and/or its treatment was causally associated with RBD onset in 9.4% of our series, but seven of nine cases had a definite organic origin: cessation of ethanol, amphetamine, cocaine abuse, fluoxetine treatment of obsessive-compulsive disorder,71 and rapid imipramine withdrawal.72 Two patients developed RBD coincident with major stress that evolved into an Adjustment Disorder—a divorce, and a frightening auto accident without physical injury.72,73 Two other cases have been reported of major stress precipitating RBD after a sea disaster,74 and after a public humiliation.75 Pharmacotherapy can induce RBD or aggravate pre-existing RBD. The most common offending agents are antidepressants such as fluoxetine, venlafaxine, or tricyclic antidepressants.5 Bupropion, a dopaminergic and noradrenergic antidepressant, may be the agent of choice in treating depression with RBD.

16. Categorization of Neurologic Disorders. A diverse set of disorders was reported to be causally linked to RBD onset, with neurodegenerative disorders (especially parkinsonism) and narcolepsy being the most common. Among the neurologic disorders, a neurodegenerative disorder was present in 48% of our series, in 73% of the Mayo Clinic series, and in 92% of the Strasbourg series. In all three series, Parkinson’s disease and Multiple System Atrophy (MSA) were by far the most common degenerative disorders, with other cases involving Progressive Supranuclear Palsy, Shy-Drager syndrome, and olivopontocerebellar degeneration (OPCD). Dementia with or without parkinsonism was found in 22% of our series, and dementia without parkinsonism was found in 13% in the Mayo Clinic series. Cerebrovascular disease,5,76,77 brainstem tumors,5 multiple sclerosis,78 and various other conditions can also be associated causally with RBD.5 It should be noted that virtually all the neurologic disorders known to be associated with RBD can also manifest as “subclinical RBD” (or “pre-clinical RBD”), with loss of REM-atonia and/or excessive phasic EMG twitching in REM sleep—with or without associated minor behaviors or sleepwalking; subclinical RBD can also be a (presumed) idiopathic condition.5 Sleep bruxism has been reported to be a subclinical manifestation of RBD.65 Japanese investigators have reported on studies of idiopathic RBD,80,81 and on studies of RBD emerging with various neurodegenerative disorders.5,82,83

Differential Diagnosis

RBD is one of several disorders that can manifest as violent sleep-related and dream-related behaviors, which can closely mimic RBD—and which serve as compelling reasons for requiring overnight, attended PSG monitoring to establish the diagnosis of RBD. Other disorders include sleepwalking and sleep terrors,73,84-86 nocturnal seizures,87-93 episodic nocturnal wandering,94,95 hypnogenic paroxysmal dystonia,96 obstructive sleep apnea (OSA) with agitated REM-related arousals,73,97-100 rhythmic movement disorders of NREM and REM sleep,101,102 nocturnal psychogenic dissociative disorders,73,103 and malinger 104 “Pseudo-RBD” has been reported in five cases of OSA-induced arousals from REM sleep, with dream-related complex and violent behaviors.99 A 69 year old man presented with a history of EDS and dream-related behaviors, such as turning the pages of a newspaper or screwing in a light bulb. A 68 year-old man with a history of loud snoring and EDS had several episodes...
of hitting his wife in bed during attempted dream enactment while dreaming that he was in a fight. A 67-year-old man had a history of EDS and abnormal nocturnal behaviors in which he would shout, grab, and injure his wife while dreaming of prior military experiences and of sporting events. A 52-year-old man had a progressive disorder of EDS and nocturnal dream enactment, where he would throw out punches and kick repeatedly while dreaming that dogs were biting his leg. A 51-year-old man would fall out of bed while asleep, and put his fist through a window. The PSGs of all 5 patients were diagnostic of OSA, but not for RBD. The apnea-hypopnea index ranged from 51-196 per hour, oxygen saturation nadirs ranged from 68%-82%, and sleep efficiency ranged from 30-79%. Three patients treated with nasal CPAP had resolution of their pseudo-RBD with control of OSA. It thus appears that in OSA, obstructive apnea-induced arousals from REM sleep with vivid dreaming can result in immediate, post-arousal, dream-enacting behaviors with locomotion, agitation and violence. This state could be called an obstructive apnea-induced, hypnopompic REM parasomnia that closely resembles RBD. Four additional patients with OSA and pseudo-RBD have been briefly described, with their PSGs showing “severe OSA and normal atonia during REM sleep.” We reported the case of a 79-year-old man with a two year history of injurious dream-related behaviors, with oxygen nadirs of 80% during REM sleep. Guilleminault and Silvestri have demonstrated how OSA induces agitated, delirious arousals with ambulation.97

Sleepwalking and sleep terrors in adults can present as injurious dream-enacting behaviors. Putative covert REM sleep processes inducing dream generation in NREM sleep, as hypothesized by Nielsen,105,106 may be especially relevant to the dream-enacting behaviors found in adult SW/ST. Nocturnal psychogenic dissociative disorders can also present with injurious dream-enacting behaviors, with the perceived dreaming occurring during established EEG wakefulness, as documented by PSG monitoring.73,103 The typical scenario involves a variable amount of sleep, followed by an EEG awakening without behavioral activation (the patient continues to lie still in bed with eyes closed, as if remaining asleep), and then 30-90 seconds later will start enacting a “dream” which often is a memory of a past abuse scene, such as being physically or sexually abused by a sibling or parent.

Nocturnal seizures can manifest as recurrent abnormal dreams, nightmares, and dream-enacting behaviors—including violent behaviors. A dramatic example of nocturnal seizure pseudo-RBD involves a 65-year-old man with the sudden onset of frequent nightmares and dream-related behaviors precipitated by a right temporal lobe infarction.87 In a typical episode, “he would suddenly bolt upright, pace around with a terrified expression on his face, and shout in a dysarthric voice…At times he related frightful visions (men coming into his room), and occasionally would give vivid details.” PSG showed that no episode emerged from REM sleep, but typically from stage 2-3 sleep, “with approximately 20 seconds of EEG evidence of awakening while the patient remained behaviorally asleep. The episode of abrupt movements and shouting then obscured the EEG record.” (This latter description is virtually identical to what is found during PSG monitoring of patients with nocturnal dissociative disorders, as mentioned above). Anti-convulsant therapy, with diphenylhydantoin, of these stroke-induced, complex partial seizures produced complete remission of all symptoms, including nightmares and dream-related behaviors. In a related report,88 a 58-year-old man had a six-year history of vivid dreaming associated with ambulation and screaming; one time he awakened while striking the molding around his bedroom window. PSG revealed “frequent repetitive polyspike discharges…in REM sleep accompanied by generalized clonic activity lasting up to 20 seconds. Frequent brief myoclonic jerks were also noted during REM sleep…After the longest episode he mumbled and made purposeful movements…Otherwise REM atonia was maintained.” In another report,89 a 16-year-old male experienced recurrent purposeful movements, cursing, and “auto-aggressive behavior” during sleep, with some subsequent recall of these episodes; PSG revealed slow spike-and-wave activity arising from REM sleep. Anti-convulsant therapy, with carbamazepine, completely resolved his sleep-related problems. The case of a 7-year-old girl has been reported,90 who presented with a six-month history of episodic nocturnal agitation occurring two to three times nightly, in which she would pull her hair and hop around her bed, and at times she recalled dreams that were congruent with her behaviors. She had sustained ecchymoses and lacerations from her violent parasomnia. During PSG, she had seven seizures between 05:00 hour and 07:00 hour, initiated by bifrontal rhythmic EEG activity, that arose primarily from REM sleep, with rolling from side-to-side, sitting up, and hopping on the bed. One behavioral spell had associated dreaming. Treatment of the complex partial seizure, of frontal lobe origin, with carbamazepine resulted in
immediate and sustained control of the nocturnal seizures. (Previous treatment with clonazepam had induced partial and temporary reduction of symptoms). The authors correctly state that in their patient, “a clinical event during routine [PSG] could be misconstrued as REM behavior disorder, unless an extended EEG montage was utilized.” Exclusive REM sleep-related complex partial seizures were documented in 16% of a series of 50 patients with complex partial seizures. Finally, patients with temporal lobe epilepsy and recurrent abnormal dreaming have demonstrated temporal lobe spike EEG activity during REM sleep.

Parasomnia Overlap Disorder

Our center has reported on a group of 33 RBD patients with PSG-documented overlapping NREM-REM sleep motor parasomnias consisting of sleepwalking, sleep terrors, and RBD. Mean age was 34 years (range: 5-72); mean age of parasomnia onset was 15 years (range: 1-66); and 70% (n=23) were males. An idiopathic subgroup (n=22) had a significantly earlier mean age of parasomnia onset (9 years; range: 1-28) than a symptomatic subgroup (n=11) (27 years; range: 5-66), whose parasomnia began with either neurologic disorders, n=6 (congenital Mobius syndrome; narcolepsy; multiple sclerosis; brain tumor [and treatment]; brain trauma; indeterminate disorder [exaggerated startle response/atypical cataplexy]); nocturnal paroxysmal atrial fibrillation, n=1; post-traumatic stress disorder/major depression, n=1; chronic ethanol/amphetamine abuse and withdrawal, n=1; or mixed disorders (schizophrenia; brain trauma; substance abuse), n=2. The rate of psychiatric disorders was not elevated; group scores on various psychometric tests were not elevated. Forty-five percent (n=15) had previously received psychologic or psychiatric therapy for their parasomnia, without benefit. Treatment outcome was available in 20 patients; 90% (n=18) of whom had substantial parasomnia control with bedtime clonazepam (n=13), alprazolam and/or carbamazepine (n=4), or self-hypnosis (n=1). This series of cases thus demonstrated striking motor-behavioral dyscontrol extending across NREM and REM sleep. Various other (diverse) cases of parasomnia overlap disorder have been reported, including cases of subclinical RBD associated with injurious SW.43,98,108-111 Spontaneous cases of parasomnia overlap disorder have been described in dogs and cats brought to a university veterinary clinic.40 An experimental animal model crucial for understanding parasomnia overlap disorder—in conjunction with the pontine lesion animal RBD model of Jouvet and Delorme—consists of Kitsikis and Steriade’s cat model of kainic acid injection into the midbrain reticular core.112 There was the immediate induction of hallucinatory defense-attack behavior during an activated, wakeful EEG that was identical to the REM sleep behaviors elicited by Jouvet and Delorme in pontine-lesioned cats.3 The abrupt onset of problematic, hallucinatory behavior with wakeful EEG in this cat model may have a counterpart in human adult disorders of arousal (SW, ST).

Association with Narcolepsy

A close association of RBD with narcolepsy has been described in two reports. In the first report, combined narcolepsy-RBD was documented in a series of 10 cases (80% male); mean age of narcolepsy onset was 23+15 years (range: 12-59), and mean age of RBD onset was 29+17 years.113 RBD emerged in tandem with narcolepsy in five cases, and early in the course of narcolepsy in three cases. Treatment of cataplexy with tricyclic antidepressants either induced or aggravated RBD in three cases. An additional seven patients had subclinical RBD. For the entire group of 17 RBD and subclinical RBD patients, 71% were male and the age range was 8-74 years. Thus, RBD can be regarded as an additional REM sleep abnormality within the narcolepsy syndrome. In the second report,114 records of 14 narcoleptic patients with RBD were retrospectively analyzed in a controlled design, and the (testable) suggestion was made that sleep motor dyscontrol in narcolepsy may start as a NREM sleep parasomnia in childhood and then “the onset of narcolepsy might represent the turning point for its intrusion into REM sleep.”

There have been other reports of RBD, with tonic and/or phasic EMG abnormalities during REM sleep, associated with narcolepsy and its treatment.115-117 In one report, clomipramine treatment of cataplexy induced agitated and violent sleep behaviors that were documented by PSG to occur within REM sleep: “interestingly enough, no activity at the submental muscle could be seen” (i.e., there was full preservation of REM-atonia in this case).115 We reported a case involving a presumed RBD episode arising from a cataplectic attack in a 55 year-old narcoleptic woman.116 A 58 year-old male with narcolepsy and emergence of RBD after five years of clomipramine treatment of cataplexy, developed obstructive sleep apnea syndrome shortly after initiating clonazepam treatment of RBD, which disappeared upon discontinuation of clonazepam, as documented by serial PSG studies.117

Association with Specific HLA Haplotypes

Narcolepsy, like RBD, is a multifaceted disorder involving REM sleep dysregulation, including REM sleep motor dysregulation. Narcolepsy has a very strong association with HLA class II genes, with the DQB1*0602 (DQw1 group) allele being expressed in nearly all cases. We conducted a study of HLA class
II antigen phenotyping in a group of 25 Caucasian males who had RBD but not narcolepsy: 84% (n=21) were DQw1 (DQB1*0506) positive (and 28% [n=7] were DR2-positive); DQB1*0501 (n=9) and DQB1*0602 (n=7) were the most common phenotypes (118). The 84% DQw1 rate in RBD was significantly greater (p=.015) than the 56% DQw1 rate found in a local Caucasian comparison group (n=66), and was greater than the 39%–66% DQw1 rates in 12 published Caucasian groups (n=40–418 per group). In contrast to the nearly 100% DQw1-DR2 linkage in narcolepsy, only 28% of RBD patients in this report were DR2-positive. The strong dissociation between DQw1 and DR2 in RBD can be contrasted with the very strong DQw1-DR2 association in narcolepsy. Narcolepsy and RBD, therefore, have strikingly convergent (DQw1) and divergent (DR2) HLA findings.

These data raise the question of whether RBD is, in part, an autoimmune disorder. We conducted a controlled study of 10 RBD patients which did not detect antibodies to the Locus Ceruleus. Additional studies searching for autoimmunity in RBD need to be conducted. Narcolepsy is presumed to be an autoimmune disorder, with the autoimmune target being the hypocretin/orexin neurons in the lateral hypothalamus. A case of autoimmune, severe insomnia (“agrypnia”) and dysautonomia has recently been reported in a 55 year old woman with serum and CSF antibodies to GABA-ergic synapses; immunosuppressive therapy and plasma exchange restored normal sleep and controlled the dysautonomia.

Association with Parkinsonism and Other Extrapyramidal Disorders

Cumulative findings from various centers strongly suggest the following: 1) there is a common co-existence of RBD and subclinical RBD with parkinsonian disorders; 2) RBD may be the initial manifestation of a parkinsonian disorder in a substantial number of RBD cases initially considered to be idiopathic; 3) Lewy body pathology, and striatal dopamine transporter dysfunction, may be quite prevalent in idiopathic RBD, and perhaps also in subclinical RBD; and 4) a compelling and testable hypothesis has been put forward that the association of RBD with neurodegenerative disease may preferentially reflect an underlying synucleinopathy, to be discussed.

The delayed emergence of a parkinsonian disorder in RBD has been reported in a group of 29 male patients >50 years of age at our center who were initially diagnosed to have idiopathic RBD. Thirty-eight percent (11/29) eventually developed a parkinsonian disorder (presumably Parkinson’s disease [PD]) at a mean interval of nearly four years after the diagnosis of RBD, and at a mean interval of nearly 13 years after the onset of RBD. Thus, RBD can be the heralding manifestation of PD, by many years, in a substantial subgroup of older male RBD patients. It is possible that a number of presumed PD patients could eventually develop Multiple System Atrophy (striatonigral degeneration subtype). The need for serial neurologic evaluations after the initial diagnosis of idiopathic RBD is evident from these data.

In another report, presumed RBD preceded the onset of PD by 4-5 years in three elderly male patients, and both the PD and RBD were ameliorated by levodopa therapy. Two preliminary studies suggested that RBD and subclinical RBD may be quite prevalent both early and late in the course of PD.

In a report of PSG findings in 10 non-depressed, non-demented PD patients, five with and five without dopaminergic treatment-induced hallucinations, RBD was diagnosed in 50% (n=5) of the total group (in four of the five non-hallucinators). Mean age of the total group was 68 years, and 70% (n=7) were male.

Lewy body disease, as a postmortem finding, was reported in an 84 year-old man with a 20 year history of RBD, but without any clinically-detected neurologic disorder. Postmortem histopathologic examination revealed that the patient had Lewy body disease with marked decrease of pigmented neurons in the locus ceruleus and substantia nigra, suggesting that Lewy body disease may underlie “idiopathic” RBD in elderly patients.

Dementia of the Lewy body type was clinically diagnosed, based on recognized operational criteria, in a case of a 73-year-old man with a two year history of parkinsonism and a 15 year history of RBD. The clinical course contained a mix of parkinsonian symptoms, dementia with fluctuating cognitive performance, and intermittent psychotic symptoms.

Probable diffuse Lewy body dementia was reported in a 72-year-old man with a 17-year history of RBD and a two year history of dementia. The patient typically had a placid disposition during the daytime, but would attack his wife and attempt to choke her during sleep. Cognitive dysfunction began insidiously, but eventually became the dominant clinical concern. He subsequently developed visual hallucinations and illusions and often thought his wife was an imposter. There was marked fluctuation of cognitive capacities.

Another case was reported of an elderly male patient with the Lewy body variant of Alzheimer’s disease (AD) identified by postmortem ubiquitin staining.

The potentially close association between Lewy body disease and RBD has been further explored in a recent study entitled, “REM Sleep Behavior Disorder and Degenerative Dementia: An Association Likely Reflecting Lewy Disease.” A group of 37 patients (92% male) with degenerative dementia and RBD was evaluated. Two subgroups were compared: one group (n=20) with two or more clinical signs of parkinsonism; the other group (n=17) without parkinsonism. RBD had emerged prior to, or concurrently with, the onset of dementia in 95% (35/37) of patients, with mean age of RBD onset being 61 years and mean age of dementia onset being 68 years. The clinical features of RBD and dementia in both groups were remarkably similar, with fluctuating cognitive status (cognition/alertness) and visual hallucinations being common. There were no significant differences in the frequency of clinical features or in neuropsychological performance between patients with and without parkinsonism. Diffuse Lewy body disease was diagnosed, according to established criteria, in 92% (34/37) of all patients. Three patients were autopsied, with all three demonstrating limbic Lewy body pathology, with or without neocortical Lewy body pathology.

The Mayo Clinic group then published findings from a study aimed at determining whether the dementia associated with RBD differed from Alzheimer’s disease (AD). The retrospective study compared neurocognitive performance between 31 patients with degenerative dementia and PSG-confirmed RBD and 31 patients with autopsy-confirmed AD, but without brainstem Lewy body pathology. RBD preceded the onset of cognitive decline in 24 patients and coincided with cognitive decline in five patients, for a total of 94% (29/31). There were major formal neurocognitive differences between the two groups: the
RBD/dementia group had significantly worse scores in attention, perceptual organization, visual memory, and letter fluency; whereas the AD group had significantly worse performance on confrontation naming and verbal memory. Most of the RBD/dementia group also met criteria for possible or probable Diffuse Lewy Body Disease. Thus, the cognitive and clinical data indicate that the dementia associated with RBD may represent Diffuse Lewy body disease.

The Mayo Clinic group has recently put forward the hypothesis that dementia/neurodegenerative disease associated with RBD most likely reflects an underlying synucleopathy, which encompasses Parkinson’s disease, multiple system atrophy, and dementia with Lewy bodies.100 Whereas there are a number of published neuropathological reports of RBD associated with synucleopathies, to date there are no such published reports of RBD associated with a “tauopathy,” which encompasses pure AD (without coexisting Lewy bodies), Pick’s disease, frontotemporal dementia, primary progressive aphasia, progressive supranuclear palsy, corticobasal degeneration, and posterior cortical atrophy. The synucleopathies share the common feature of alpha-synuclein in positive intracellular inclusions, whereas the tauopathies share the common feature of hyperphosphorylated tau protein within neuronal microtubules.100

Shy-Drager syndrome (SDS) presenting as RBD has been reported in an elderly male.134 RBD had emerged violently at age 53 years, as he punched, choked, kicked, and spat on his wife while dreaming of being attacked. His waking behavior, however, remained unchanged and he was described as “a loving and caring husband and father and retained his job as a public relations executive. His mood was reported as ‘good’ and his affect was euthymic.” A physical examination at the time of RBD onset was unremarkable—with the notable exception of a 40 mm Hg asymptomatic orthostatic drop in systolic blood pressure. SDS insidiously emerged five years after the onset of RBD. The presenting symptom of multiple system atrophy (MSA) was reported to be RBD in two male cases, with RBD emerging at ages 42 and 57 years, and MSA (striato-nigral and olivo-ponto-cerebellar sub-types) emerging two or three years subsequently.135 In a large systematic study involving 39 consecutive MSA patients (mean age, 60 years, range: 43-80; 67% male), RBD was diagnosed by PSG monitoring in 90% (n=35) of these patients (136). Dream-enacting behaviors were reported in 69% (n=27) of patients. In 44% (n=12) of this subgroup, RBD preceded the clinical onset of MSA by more than one year; in 26% (n=7) of this subgroup, RBD and MSA emerged concurrently; and in 30% (n=8) of this subgroup, RBD emerged more than two years after the appearance of the first MSA signs. Thus, RBD is the most common clinical sleep disorder in patients with MSA, and RBD can often herald MSA signs and symptoms by years. REM sleep-related sleep talking was documented during PSG monitoring in 86% (n=18) of a series of 21 patients with MSA, and in these patients, sleep talking had begun or had intensified at the time of clinical onset of MSA.137 Excessive amounts of REM sleep without atonia were documented in all but one patient, and excessive motor activity (apart from sleep talking) during REM sleep was documented in all but two patients, and involved cranio-facial, oro-facial or limb movements.

The relationship of sleep attacks, psychotc episodes, and parkinsonism disorders has recently been reconsidered, with several hypotheses raised:138 Could sleep attacks in parkinsonism be REM intrusions, and “psychosis” be the intrusion of dream imagery into wakefulness? Could drop attacks seen in Lewy body dementia be cataplectic episodes? Could late-onset narcolepsy, with or without RBD, represent an evolving parkinsonian disorder?

**Brain Mechanism Underlying Symptomatic and Idiopathic RBD: Focus on the Extrapyramidal System**

The growing awareness of a strong association between RBD and extrapyramidal disorders raises the critical question as to what brain mechanisms underlie REM motor dyscontrol with extra-pyramidal disorders? The pedunculopontine nucleus (PPN) in the upper brainstem is likely to be prominently involved in the disruption of the REM-atonia circuitry, for at least three reasons: First, there is a strong reciprocal connectivity between the PPN and the substantia nigra,139 the main site of pathology accounting for the cardinal signs of PD. In fact, “antero- posteriorly”, the PPN actually merges with the posterior part of the dopaminergic substantia nigra.140 Second, the neuropathology of PD includes prominent neuronal loss within the PPN.141 Third, the PPN has strong links with both the REM-atonia and REM-phasic generator circuitry.138,142-143 The retrorubral nucleus, which is likely to be involved in the REM-atonia circuitry, is located near the substantia nigra, and may thus be implicated in the linked PD-RBD pathology.142 In addition, the substantia nigra also is closely connected to the REM-phasic generator circuitry and may play a major role in the genesis of PGO waves, a characteristic REM sleep phasic event.144 In regards to MSA, pontine involvement was revealed by both gross neuropathologic examination and histochemical studies, as cited by Plazzi et al.136

Studies in dogs have identified a co-localization of the atonia and locomotor systems in the pons, thus providing an anatomic basis for the simultaneous dysregulation of the tonic and phasic motor systems in RBD.142

Rye of Emory University has provided a comprehensive framework for considering the crucial role that the PPN appears to play in the pathophysiology of RBD.145 His report—which impressively integrates a large body of work from disparate neuroscientific fields to help elucidate the role of the PPN and the laterodorsal tegmental nuclei (the two brainstem cholinergic centers) in state-dependent normal and pathological behaviors—later prompted a state-of-the-art dialogue with Morrison.146-147 In his report, Rye hypothesized that “a subpopulation of dopamine-responsive neurons in the PPN innervate a ventral medullary region widely recognized to modulate atonia...particularly atonia that accompanies REM sleep.”145 Furthermore, he cites the meticulous work of Chase and Morales in determining that glutaminergic and cholinergic neurons in the “midbrain extrapyramidal area” (MEA) and PPN play crucial roles in maintaining the atonia of REM sleep.148,149 Additionally, “neurons overlapping in distribution with the MEA display REM sleep-specific increases in neural discharge, project to medullary regions essential in maintaining REM atonia, and, when lesioned, release complex motor behaviors in REM sleep in animals.” Rye buttressed his argument in part with the comment that human RBD is responsive to dopaminergic agents.145,147 However, this statement has minimal documentation in the literature, and ignores the well-documented therapeutic efficacy of clonazepam, as already reviewed in a previous section. Dopaminergics are included in a...
rather long list of agents that may be used to treat human RBD if clonazepam is ineffective or not well tolerated. Since clonazepam is a potent benzodiazepine with GABAergic properties, Rye could incorporate this therapeutic agent within his hypothesis that “much of the GABAergic basal ganglia output targets glutamatergic RRF and/or MEA neurons, which, in turn, activate the ventromedial medullary zone that promotes REM atonia.” Furthermore, the behaviors released in the animal model of RBD “probably also damage axons stemming from structures normally suppressing locomotor drive in REM [sleep], in addition to those inhibiting alpha motor neurons.” Rye’s response to Morrison’s comments contained several key components.

In Morrison’s response to Rye’s report, he emphasized that “no one has provided convincing evidence that limited lesions will release all of the behaviors that one can observe during the phenomenon of REM without atonia in cats.” Furthermore, the behaviors released in the animal model of RBD “probably also damage axons stemming from structures normally suppressing locomotor drive in REM [sleep], in addition to those inhibiting alpha motor neurons.” Rye’s response to Morrison’s comments contained several key components.

In a collaborative study with Garcia-Rill and Skinner from the University of Arkansas, we tested the P1/P50 midlatency auditory evoked potential in 22 older males with chronic RBD and controls. The P1 potential measures sensory gating, and appears to be generated, in part, by the PPN. As a group, the RBD patients did not differ from the control group; however, when patients with RBD and PD or RLS (RBD+) were compared to patients with idiopathic RBD alone, there were significant differences in P1 potential habitation at both the 500 and 1000 msec inter-stimulus intervals (ISIs). Also, the RBD+ group differed significantly from the control group at the 500 msec ISI. The authors concluded that the difference in P1 potential disinhibition between RBD subjects seems more related to their combined movement disorders rather than to their RBD per se.

**Juvenile and Adolescent RBD and Developmental Considerations**

Idiopathic and symptomatic RBD, as well as sub-clinical RBD, have been reported in children and adolescents, beginning as early as 11 months of age. Idiopathic RBD—within complex behaviors accompanied by vivid dreaming and nightmares—was documented in four of five children in a reported series (mean age, nine years; gender not reported), with the other child having RBD associated with narcolepsy. All five patients were successfully treated with clonazepam, 0.25 mg at bedtime. Clinical and subclinical RBD with narcolepsy has been documented by our center in five cases (all male) in children and adolescents (aged 8,12,13,17,19 years), and in two cases from other centers, involving RBD in a 16-year-old narcoleptic.
male, and subclinical RBD in a 7-year-old narcoleptic female. RBD has also been documented in two girls (aged 8, 10 years) with brainstem tumors. The 8-year-old brother of one of these girls also demonstrated prominent aperiodic EMG twitching and gross movements during both REM and NREM sleep (as did his sister with RBD), although neither of them had any PLMs, which the father had on PSG, but he did not have aperiodic EMG twitching nor any behaviors. Two cases of early childhood RBD associated with the “hereditary quivering chin syndrome” have been described by the same group of investigators; both were males, 18 and 22 months of age, with onset of RBD as early as 14 months of age. One child had “violent jerking, agitated crawling and loud vocalizations” during his sleep at home, and during his PSG he crawled and vocalized during REM sleep. The other child had vigorous body movements during REM sleep. Both boys had loss of REM atonia, with one also having notably enhanced REM phasic motor activity. RBD was controlled in both boys with bedtime clonazepam, which also controlled problematic tongue biting in one of the boys. The quivering chin syndrome is thought to be related to dysfunction in the pons or medulla, which could also account for the coexistence of RBD in these cases. A case of RBD associated with PD and pontocerebellar degeneration has been reported in an 18-year-old African American female. Although the PD and narcolepsy began at the age of 16 years, it is not clear when the RBD began. Subclinical RBD has been documented in a 17-year-old male with olivopontocerebellar degeneration.

RBD (n=3) or subclinical RBD (n=9) was identified in 75% (12/16) of patients (age range, 6-65 years; n=14 male) with Tourette’s syndrome in a retrospective study. Both tonic and phasic EMG abnormalities were detected during REM sleep. Prospective studies, with age stratification, are needed to replicate these provocative findings on RBD linkage with Tourette’s syndrome. Subclinical RBD was documented by PSG in a controlled study of 13 patients (six males, seven females) aged 11-39 months with Group A xeroderma pigmentosum, a disorder characterized by extreme sensitivity to sunlight, a high incidence of skin cancer, and a primary neuronal degeneration, affecting both the peripheral and central nervous system, with a slowly progressive course. Both tonic and phasic EMG abnormalities were detected during REM sleep in all these patients, suggesting a pathological brainstem substrate for both their neurologic disorder and their REM sleep motor abnormalities. Subclinical RBD with prominent phasic motor disinhibition during REM sleep has been found in a controlled study of 11 patients (aged 60-83 weeks; six females, five males) with infantile spasms (West syndrome). In summary, juvenile and adolescent RBD and subclinical RBD mirror their adult counterparts in many respects, even though prevalence rates may be lower for a number of associated conditions.

In regards to developmental predispositions for RBD and subclinical RBD, we stated in our 1986 report that “in humans, REM sleep becomes recognizable between the 27th and 30th week of gestation. From the outset and extending through infancy, there are prominent REMs, limb jerks, and simple oro-facial behaviors. Other mammals demonstrate comparable early developmental phenomena, which may reflect a maturational lag in CNS inhibitory capacity.” The seminal work of Corner, of the Netherlands Institute for Brain Research, on spontaneous motility patterns of rat pups and chick embryos is crucial to understanding the developmental foundations for various aspects of human RBD, including childhood RBD/subclinical RBD, the long prodrome of adult RBD, etc., (e.g., “neonatal spinal rats exhibit spontaneous twitching which appears to be phenomenologically indistinguishable from the motility which, in intact rat pups, is conventionally used for identifying Active [REM] Sleep as a behavioral state. In turn, this early sleep behavior strongly resembles spontaneous movements displayed by the late rat fetus. As in the chick embryo, phasic motility in mammals therefore probably begins as endogenous (i.e., nonreflexogenic) spinal interneuronal discharges…” Corner goes on to state that “since repetitive bursting patterns are typically displayed also by embryonic spinal cord and lower brainstem neurons—whether derived from mammalian, avian or amphibian species—even when isolated and cultured in vitro, neurophysiological patterns such as these could represent the basis for the earliest vertebrate behaviors...[that] is further suggested by the presence of strikingly similar neuromotor patterns in the nerve nets of coelenterates...the source of excitory drive underlying early nonreflexive behavior patterns seems most likely to lie within the reticular core of the entire central nervous system.” Corner also provided a “rope analogy” diagram for representing the multi-stranded physiologic phenomena of (REM) sleep in mammals, with component processes (body twitches, sucking movements, REMs, EMG tone, breathing patterns) initially appearing with independent rhythmicities that gradually coalesce into a recognizable set of state parameters. Corner’s rope analogy, first put forth in 1984, also foreshadowed adult RBD, since the rope unravels in old age, with component processes separating from one another, allowing for dissociated states. In this context, RBD can be understood as a disorder in which intrinsic phasic motility patterns present in normal early development reemerge late in life in a pathologic state. It is impressive how the phasic EMG bursts of intrinsic motility patterns are indistinguishable from those of RBD, and can be superimposed on one another (as demonstrated by Corner and Mahowald in their presentations at the First World Federation of Sleep Research Societies, Cannes, France, September 1991). Finally, Corner has recently written a comprehensive, and integrative, review of the field of neuroplasticity and the field of intrinsic biorhythm generators of neuromotor activity. Central to this review is a discussion of experimental manipulations of glutaminergic synaptic transmission and NMDA receptor activity (e.g., experimental blockade), which is relevant to a further understanding of RBD, particularly in light of the elegant work by Siegel and Lai on these neurotransmitter/receptor systems that mediate locomotion and muscle atonia in the brainstem.
colleagues is also pertinent to this topic, as they have brought together compelling data pertaining to the ontogenetic function of REM sleep to buttress their hypothesis that REM sleep processes (especially phasic activity) direct the course of brain maturation in early life through the control of neural activity.181

**Agrypnia Excitata**

The term has recently been utilized by Lugaresi and Provini from the University of Bologna to describe the unifying features of three seemingly disparate conditions—fatal familial insomnia (FFI), Morvan’s chorea, and delirium tremens—which share the core clinical features of severe insomnia, absence of slow-wave sleep, dream-enactment, motor/autonomic activation, and mental confusion.182 The term “agrypnia excitata” was first used in 1931 and aptly describes this syndrome. In FFI, there is a dynamic imbalance between activating and deactivating neuronal centers in the limbic system induced by atrophy of the mediodorsal and anteroventral thalamic nuclei. In Morvan’s chorea, there is a dynamic imbalance within thalamo-limbic circuits that could result from the accumulation of anti-receptor antibodies (i.e., auto-immune response). In delirium tremens, the dynamic imbalance in these circuits could result from a transient prevalence of excitatory over inhibitory synaptic activity. The dream-enactment in these three conditions occurs during brief, recurring episodes of REM sleep that intrude into wakefulness throughout the 24 hour day, and the behaviors observed are typical RBD behaviors. Clearly, this seminal work will open up additional opportunities for exploring RBD-like oneric behaviors emerging in conjunction with various CNS autoimmune disorders, basal forebrain and other localized degenerative disorders, and various toxic-metabolic conditions.

**Melatonin Therapy of RBD**

Kunz and Bes from Berlin fortuitously discovered in 1997 that bedtime melatonin administration controlled RBD in a 64 year-old man who also had the major complaint of sleep-onset insomnia, which had prompted the trial of melatonin.183 These authors then conducted an open-label study which demonstrated control of melatonin may be less potent than that of clonazepam, in five of six patients then conducted an open-label study which demonstrated control of RBD (behavior and dream disturbances) in five of six patients. Boeve reported that melatonin controlled (symptomatic) RBD in all eight treated cases, at a bedtime dose of 6 mg (one patient took 12 mg), with four of these patients continuing to take clonazepam, 0.5 mg at bedtime.186 No side effects were reported, apart from one case with headaches. Boeve concluded that “melatonin can be considered as sole or add-on therapy for treatment of RBD associated with a variety of neurologic…disorders.” Further research is needed, including a longitudinal perspective to determine whether melatonin can maintain its efficacy, as clonazepam has demonstrated, without dosage escalation, for one or two decades.

**Status Dissociatus**

This is the most extreme form of RBD, and appears to represent the complete breakdown of state-determining boundaries.187 Clinically, these patients appear to be either awake or asleep; however, their “sleep” is very atypical, characterized by frequent muscle twitching, vocalization, and reports of dream-like mentation upon spontaneous or forced awakening. Polygraphically, there are no features of either conventional REM or non-REM sleep; rather, there is the simultaneous admixture of elements of wakefulness, REM sleep, and non-REM sleep. “Sleep” can be perceived to be “normal” and even restorative, despite the nearly continuous motor and verbal behaviors and absence of PSG-defined REM or non-REM sleep. Conditions associated with status dissociatus include protracted withdrawal from alcohol abuse, narcolepsy, OPCD, and prior open heart surgery. We also have documented an AIDS-related case with prominent brainstem involvement. Similar signs and symptoms can be seen with fatal familial insomnia, a prion disease already described. The abnormal motor and verbal nocturnal behaviors of status dissociatus may respond to treatment with clonazepam. RBD and narcolepsy are prototypic examples of state dissociation, underscoring the concept that the three states of being—wakefulness, NREM sleep, and REM sleep—are not mutually exclusive, but rather may occur in various combinations, resulting in fascinating clinical experiences and behaviors. Clearly, our states of being are not necessarily global brain phenomena. Sleep or wakefulness occurring asynchronously in bits and pieces of the brain is a useful concept. Human state dissociation has been recently extensively reviewed.187-190

**Dynamic Stabilization and Destabilization**

It is conceivable that human state dissociations may shed light upon the function of sleep. Recently, Kavanau has proposed that fatal familial insomnia (FFI), a prion disease, may be the result of lack of dynamic stabilization of the central nervous system which normally occurs during sleep.191 He contends that in FFI, the progressive loss of sleep interferes with the suspension of sensory processing, and progressively reduces non-sensory dynamic stabilization. The end result is the lack of maintenance of neuronal network integrity. Therefore, the symptoms of FFI, other than insomnia, are due to widespread insufficiencies of dynamic stabilization. Support for this hypothesis is that these symptoms are not seen in other prion diseases (unaccompanied by insomnia), and therefore may be a direct consequence of the insomnia (failed dynamic stabilization) per se. The absence of sensory...
Continuous use.192-195

NREM sleep. They do not require REM sleep and its non-utilitarian dynamic stabilization, as the circuitry is in virtually continuous use. As endothermy evolved, the skeletal muscle hypotonia of primitive sleep may have become insufficient to permit motor non-utilitarian dynamic stabilization to persist without interrupting sleep. As endothermy evolved, the skeletal muscle hypotonia of primitive sleep may have become insufficient to prevent sleep-disrupting skeletal muscle contractions during non-utilitarian dynamic stabilization. This may have led to the development of inhibition of skeletal muscle tone during a portion of primitive (NREM) sleep. REM sleep may have evolved through modifications of a fraction of NREM sleep, driven primarily for suppression of disruptive movements in sleeping endotherms during reinforcement of motor circuits by dynamic stabilization. Support for this theory is that constantly swimming marine animals engage only in unihemispheric NREM sleep. They do not require REM sleep and its non-utilitarian dynamic stabilization, as the circuitry is in virtually continuous use.192-195

Future Directions

1. A study of Hypocretin/orexin levels in the cerebrospinal fluid (CSF) of RBD patients can test the question of whether there are elevated HCRT levels in RBD, a disorder of increased muscle activity during REM sleep, which is the exact opposite of cataplexy/narcolepsy, a disorder of low HCRT brain levels120 and excessive atonia during frequent dissociated REM sleep intrusions into wakefulness.

2. Since it is now seems that “idiopathic RBD” does not really exist, it is important to perform postmortem brain analyses of patients who died while still diagnosed with “idiopathic RBD,” to look for brainstem or forebrain structural abnormalities, evidence of cerebrovascular disorder, excessive Lewy body deposits/alpha-synuclein accumulation, etc. Analysis of HCRT receptor density should also be considered.

3. We would strongly suggest that the terms “Animal RBD” and “Animal Subclinical RBD” be used in the clinical and experimental animal literature, for two reasons: 1) it would form a common terminology with its human counterpart; and 2) the currently used term in animals, “REM without atonia” can frequently be misleading, since it is also used to refer to animals with preserved REM atonia and increased phasic twitching, and it does not distinguish between clinical and subclinical RBD. The RBD/subclinical RBD terms can be further divided to distinguish among tonic, phasic, or combined tonic/phasic EMG sub-types.

4. We would urge a revision of the minimal diagnostic criteria of RBD contained in the International Classification.4 so as to include the requirement of PSG documentation of tonic and/or phasic EMG abnormalities during REM sleep, along with either documented REM sleep behaviors or a history of behaviors typical of or consistent with RBD.

5. A study of serum testosterone levels in RBD males compared to (normal sleep) controls would address one possible hormonal risk factor for RBD.

6. A costly but important study would consist of determining the prevalence of clinical and subclinical RBD in elderly males and females in the general population, and also in various clinical populations, especially in the field of neurology.

7. The strong clinical impression that most men with RBD have unusually “nice” personalities can be formally investigated, with data obtained from RBD patients being compared with those from age-matched patients having restless legs syndrome and obstructive sleep apnea, disorders of nocturnal motor agitation.

8. A longitudinal neuropsychometric study of subclinical RBD patients, and idiopathic RBD patients may indicate whether any distinctive abnormalities are present, and how they relate to the time course of RBD and eventual emergence of a neurologic disorder, in some or many cases.

Conclusion

The recognition of RBD has shed additional scientific light on parasomnias and the brain, and has opened up new areas of research on sleep, dreams, and neurologic disorders—particularly extrapyramidal disorders and narcolepsy. The vital link between basic research and clinical medicine is inherent in all aspects of RBD.

ACKNOWLEDGMENTS

This work was supported by a grant from Hennepin Faculty Associates. We acknowledge the outstanding contributions of our sleep laboratory technologists, in particular Andrea L. Patterson, the head technologist. Robert McCarley offered encouragement and assistance with our index patient. Jerry Siegel, YY Lai, Bradley Boeve, and Ilonka Eisensehr provided pertinent references. Juan Pareja and Diego Garcia-Borreguero called our attention to the passage quoted from Cervantes.

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ADDENDUM

The Lugaresi and Plazzi group has also identified that the presence of RBD can distinguish MSA with autonomic nervous system failure from pure autonomic nervous system failure. 196