

THE PARADOX OF SLEEP: THE EARLY YEARS

W.C. DEMENT

*Sleep Disorders Clinic and Research Center, and Department of Psychiatry and Behavioral Sciences,
Stanford University, Stanford, CA 94304, USA*

As we gathered in Lyon in September 2003 to celebrate the career of our esteemed colleague, Professor Michel Jouvet, we were also indirectly celebrating the field he played a major role in creating. Basic sleep research and sleep medicine are now fully established and recognized around the world as an independent and respected scientific and clinical discipline. There can be no question that the basic sleep research laboratory established by Michel Jouvet was the world's most outstanding, and that almost all individuals who subsequently became involved in basic sleep research either made the pilgrimage to this mecca or were inspired by its many contributions.

With regard to the topic of the 2003 Lyon proceedings, it seems likely that paradoxical sleep would have come under an intense scientific scrutiny sooner or later. But without the efforts of a few outstanding pioneers, maybe not. As has been stated many times, the 1953 report of the occurrence of rapid eye movements during sleep (1) was a watershed event. I agree wholeheartedly, and I cannot resist repeating what I said at the Dement/Jouvet opening ceremony at the June 2003 APSS meeting a few months earlier (prompted by Abraham Lincoln's Gettysburg address in 1863), "Two score and ten years ago Aserinsky and Kleitman brought forth on this planet a new discipline, conceived at night and dedicated to the proposition that sleep is equal to wake". On a more serious note, however, the Aserinsky and Kleitman observations should not be glibly equated with the discovery of paradoxical sleep. Clear understanding of the fundamental duality of sleep required years of scientific observation, experimentation, and conceptual breakthroughs.

Fortunately, my report (7) of the occurrence of "activated" sleep in cats in 1958 captured the interest of the Lyon group, although a little surprise, skepticism, and perhaps even scoffing intervened. The link between muscle atonia and other neurophysiological phenomenon in a variety of feline experimental preparations was demonstrated by Jouvet and his colleagues to be incredibly robust, and the pontine localization of paradoxical sleep executive functions was the beginning of the outpouring of brilliant observations and interpretations that we all know so well.

My first meeting with Michel Jouvet occurred in New York in 1960 when he visited my home which was then a combination apartment and human sleep laboratory. In 1962, he accepted the invitation to attend the second annual meeting in Chicago of the informal group that eventually became the Association for the Psychophysiological Study of Sleep (APSS). By this time, almost all of us had read the report in *Comptes Rendus* (21) and what would soon follow, the stunning breakthrough compilation that appeared in *Archives Italiennes de Biologie* (18). I will never forget the excitement of hearing his presentation at that second Chicago meeting.

I also remember talking with Michel during a break and being thrilled as he invited me to the truly epochal meeting in Lyon that took place during September 9-11, 1963 (19). As he reported at the 1963 meeting, Jouvet was well into the quest that would occupy his laboratory for many years – the elucidation of the role of monoamines in the regulation of the states of sleep (20). I very recently read through the proceedings of the 1963 Lyon meeting (19) and recalled with great nostalgia some of the outstanding individuals who were there. The participants I specially remember were Paul Dell, Ed Evarts, Raúl Hernández-Peón, Giancarlo Rossi, Giuseppe Moruzzi, Pierre Passouant, Ottavio Pompeiano, Allan Rechtschaffen, and of course Michel Jouvet himself. A number of individuals who attended the 1963 conference also participated in the September 2003 meeting. I particularly enjoyed the company of Bobby Naquet.

At this point, I wish to digress and specially applaud Michel Jouvet's (18) and Ottavio Pompeiano (28) work on understanding the mechanisms of the motor atonia associated with REM sleep which, in turn, allowed an almost instantaneous understanding of the narcolepsy tetrad. On my arrival at Stanford in January of 1963, I had immediately begun to recruit patients with narcolepsy, obtaining a huge number from an advertisement in the San Francisco Chronicle newspaper. The majority of respondents had completely unambiguous symptoms of narcolepsy. Moreover, not a single one of these victims had been previously diagnosed or treated despite an average of over five physician visits and nearly fifteen years of living with this strange illness.

In what I would consider a landmark study in collaboration with Allan Rechtschaffen and George Gulevich (13), we clearly demonstrated the association of cataplexy and sleep onset REM periods. We even succeeded in recording cataplectic attacks during which there was simultaneous H-reflex suppression and motor atonia, while breathing and the ability to move the eyes were maintained. If the patient did not enter the dream world, they could move their eyes in response to a command from the investigator.

Christian Guilleminault and I made movies of cataplectic attacks. Exhibiting these movies in various scientific meetings resulted in the discovery of (very appropriately) a French Poodle with narcolepsy whom we named Monique (23). Our group worked from 1973 until about 1993 pursuing every effort to understand the brain abnormalities in canine narcolepsy and working out the mode of inheritance. Each year, it was a daunting effort to secure grant funds from a skeptical NIH for the housing and feeding of what had become a very large colony of narcoleptic dogs. In the middle 1990's I turned the Center for Narcolepsy over to my brilliant young French colleague, Emmanuel Mignot. By this time, we completely understood that the mode of inheritance was a single autosomal recessive gene (*canarc 1*). Though the dog genome was almost entirely unknown, Mignot began searching for linkage markers and carried out an enormous amount of DNA sequencing. In 1999 almost as a miracle, the canine narcolepsy gene was isolated and found to express an abnormal receptor for the brain peptide, hypocretin, also called orexin (22). This peptide had only been characterized in 1998.

I feel that Michel and I have been lifelong transatlantic partners (Figs. 1-6). We both spent an enormous amount of our careers pursuing the Holy Grail of REM sleep. We contributed a number of chapters to the story, but today the story remains unfinished. Our main satisfaction at this point is that we have both been responsible for a number of younger sleep scientists who should have time to determine how the story will end.

For my part, in 1963 I was still clinging to my psychoanalytic beliefs (17) and had accumulated much data on selective REM deprivation in human subjects. After the 1963 Lyon meeting, I returned to Stanford determined to settle the issue of whether or not the loss of REM sleep would in some way be harmful to the organism. I was particularly impressed by what seemed to be hallucinatory behavior exhibited by Jouvet's cats with the pontine tegmentum lesions that suppressed REM sleep.

I had earlier chosen to pursue the problem of REM sleep by the approach of selective REM sleep deprivation. I had started these studies when I finished my internship in New York City. My first report (8) was titled "The effect of dream deprivation" because I still felt that REM sleep equaled dreaming sleep. At the time, I had no assistants, and the longest period that I was able to carry out selective REM deprivation was four and five nights.



Fig. 1. *The 1963 meeting in Lyon.*

Left to right: Allan Rechtschaffen, William Dement, Michel Jouvet.



Fig. 2. Michel Jovet during a visit to the Stanford University sleep laboratory.



Fig. 3. William Dement and Michel Jovet having lunch in the California sunshine.



Fig. 4. At Cornell University, Ithaca, circa 1969.

Lf to rt: Michel Jouvét, Professor James Maas, William Dement.

I continued this work as soon as I arrived at Stanford in January of 1963, and with the help of several medical students two subjects were REM-deprived for 15 consecutive nights each. The best summary of our studies of selective REM sleep deprivation in humans is actually in the published proceedings of the 1963 meeting in Lyon, *Aspects Anatomico-fonctionnels de la Physiologie du Sommeil* (9). In the human subjects, sleep onset REM periods began to appear after a relatively few nights of selective REM deprivation. When this happened, REM sleep deprivation became *total* sleep deprivation and the subjects soon became too sleepy to continue (Fig. 7).

This limitation in humans prompted us to switch to cats. It was a great advantage that we had learned so much about the use of cats in Jouvét's Lyon laboratory. Very quickly we realized that cats (and later rats and mice) could obtain non-REM sleep while sitting up and maintaining muscle tone. We made use of a "Big Bertha" treadmill that was designed by one of my students, Peter Henry (12). Two cats at a time had a sufficiently long ride on the belt toward the water tank such that they could obtain 60-90 seconds of non-REM sleep. However, this interval did not allow sufficient time for the development of the muscle atonia that indicated the onset of REM sleep. After several weeks of selective REM deprivation, the treadmill could no longer be used because the cats would walk to the front of the belt and enter REM sleep almost instantaneously. We also used the method of sitting on a platform in a



Fig. 5. At the Ohio Sleep Medicine and Neurosciences Institute, circa 1992.

Lf to rt: current National Sleep Foundation President Jim Walsh, William Dement, Institute Director Helmut Schmidt, and Michel Jouvet. Dr. Schmidt had named polysomnographic bedrooms after Walsh and Dement, but the large conference room was named after Dr. Jouvet.



Fig. 6. At the 1995 meeting of the APSS in Nashville, commemorating the 100th birthday of Professor Nathaniel Kleitman.

Lf to rt: Michel Jouvet, William Dement, Kleitman, Eugène Aserinsky.

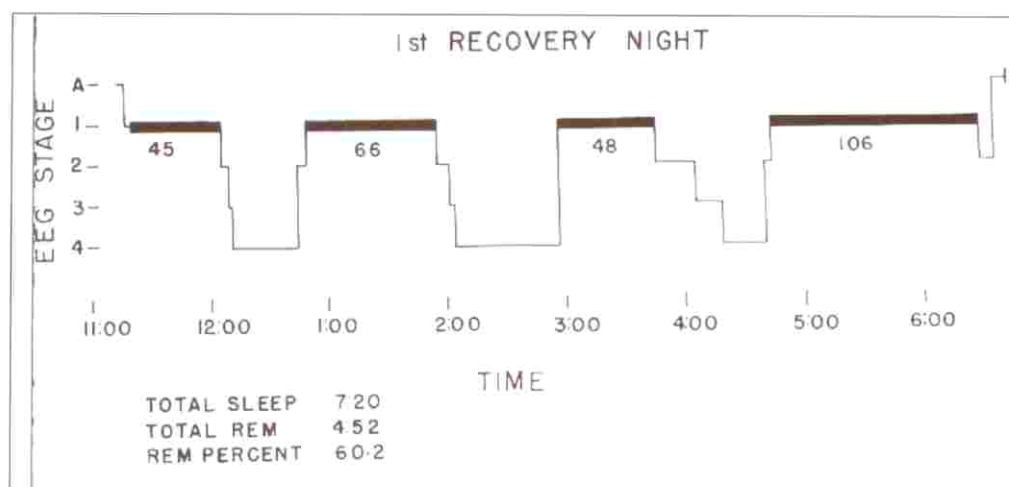


Fig. 7. First recovery night following 15 nights of selective REM deprivation in a human subject.

The time spent in REM sleep is enormously increased. Also note that REM sleep occurs at the onset of sleep.

shallow tank of water, but we could not leave cats sitting on the platform 24 hours a day.

As the number of REM onsets mounted into the hundreds, we devised the ultimate and final method of REM deprivation. The investigator would hold a cat on his or her lap while watching the polygraph and would touch the cat's nose fairly gently when EMG potentials began to disappear. At this point, attempting to interrupt REM onsets by any other approach was completely ineffective. Touching the nose, however, even though in some cases literally every few seconds, always interrupted the development of REM sleep (Fig. 8). In this way, we worked up to the eventual maximum duration of 69 consecutive days of selective REM deprivation in cats. Selective REM deprivation in rodents (rats and mice) was mainly accomplished by placing them on flowerpots (the inverted flowerpot technique that we first developed but did not report has been used many times by other investigators).

The primary and overriding goal of our selective REM deprivation studies was to demonstrate that REM sleep plays a vital role in mammalian existence. We hypothesized that a sufficiently lengthy period of selective REM deprivation would lead to the deterioration and death of the organism. We had not conceived of the strategy ultimately used by Allan Rechtschaffen and his coworkers at the University of Chicago which was to work back from the end point of death to find the crucial causal factors that led to death (30). It may fairly be said in retrospect that we were so eager to discover the gold of a vital function of REM sleep that we ignored the silver of CNS changes.

Throughout the 1960's, my group continued to work like donkeys trying to discover the function of REM sleep. We didn't take time to publish all of our studies

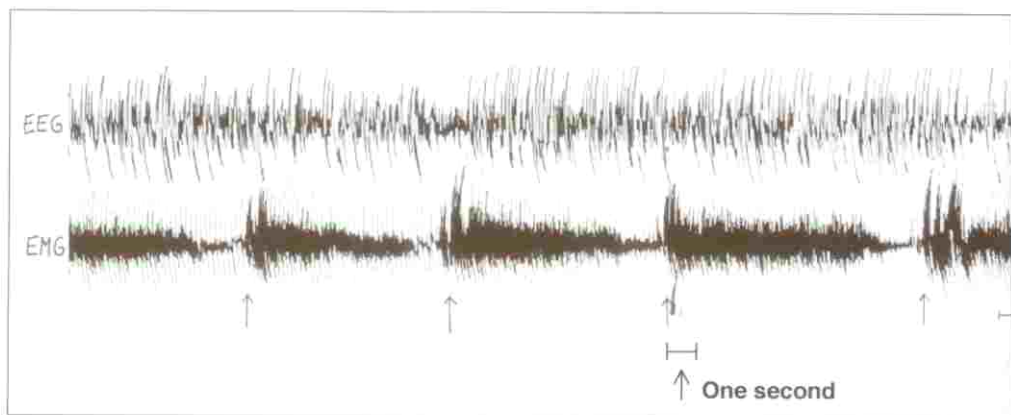


Fig. 8. Recording from a cat during prolonged REM sleep deprivation.

Each arrow indicates the moment when the investigator touched the cat's nose to prevent the occurrence of REM sleep.

but did include much of our data in book chapters and final reports for NIH grants. In reviewing this ancient material for the 2003 Lyon meeting, I have concluded that the general results obtained from the research on cats and rodents are, for the most part, still valid today. These results may be summarized as follows.

Changes in REM Sleep (11)

The percentage of REM sleep during recovery increased progressively as a function of the length of the prior period of REM deprivation (Fig. 9). Recovery sleep recordings were carried out continuously 24 hours a day until the REM sleep percentage had returned to the baseline value. In the deprivation period itself, the number of interruptions required to prevent the occurrence of REM sleep increased progressively. The most spectacular change in REM sleep was the intensification of phasic activity. This intensification was manifested by an incredible explosive vigor of muscle twitching and a huge increase in frequency of PGO waves (Fig. 10).

Changes in the waking behavior of cats (10)

The major changes can be summarized as an intensification of drive-oriented behaviors. A test for the "intensity" of food consumption was developed in which the time it took to eat a specific amount of food was the measure. This time was cut by 50 percent as the REM-deprived cats gobbled their food with a rapacity never before observed (Fig. 11). Increased aggressiveness in cats was assessed by placing them in the same enclosure with rats. Cats that ignored rodents during baseline attacked the rats ferociously when they were severely REM-deprived. Increased sexual behavior in cats (hypersexuality) was assessed by placing cats together in a large room and observing them through one-way glass (16). Cats in the baseline period

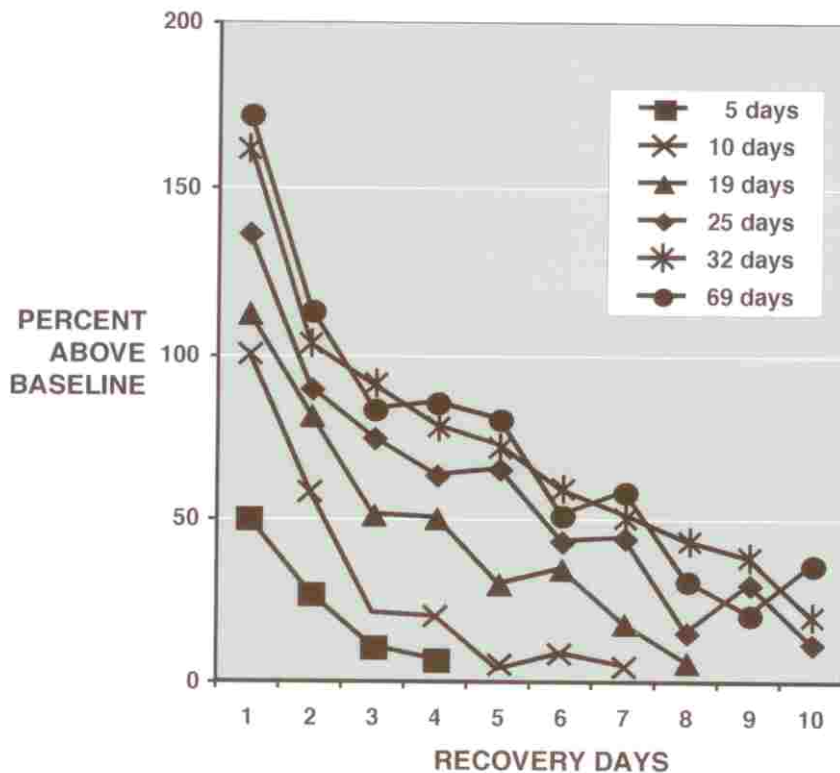


Fig. 9. Plot of progressively increased amounts of recovery REM sleep following progressively longer periods of REM deprivation in cats.

Little additional increase is seen after 30-35 days of selective REM sleep deprivation.

ignored each other; the REM-deprived cats would continuously try to mount the other cats. All of the foregoing behavioral changes were highly consistent.

Changes in the waking behavior of rats

Sexual and aggressive behavior in rats was a much more standardized and widely studied behavior and therefore subject to precise quantification. Both aggressive behavior and sexual behavior showed marked increases (24-26).

Changes in CNS

Finally, we measured certain CNS functions in the brains of cats, rats, and mice (2-6). The major approach was the assessment of electroconvulsive shock threshold. A highly significant decrease in the voltage required to induce convulsions was observed in all three species. We also were able to assess the effects of REM sleep deprivation on self-stimulation with electrodes planted in the septal area of cats and rats. The most elegant demonstration of CNS change as a result of REM deprivation

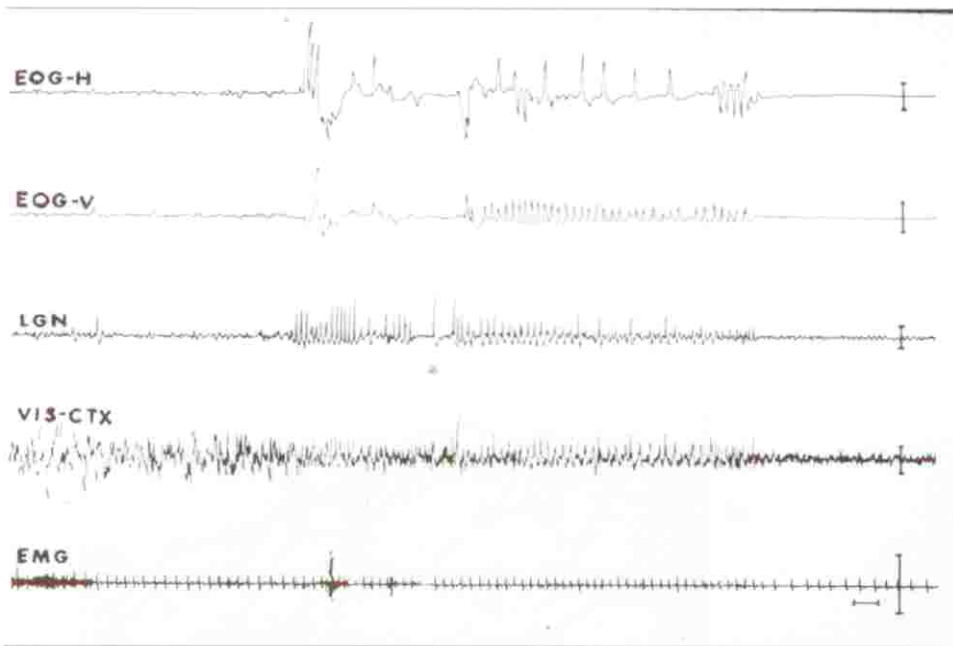


Fig. 10. Polygraphic recordings of a cat undergoing selective REM sleep deprivation.

Note the huge increase in PGO waves in the lateral geniculate nucleus, which are associated with a similar large burst of eye movements.

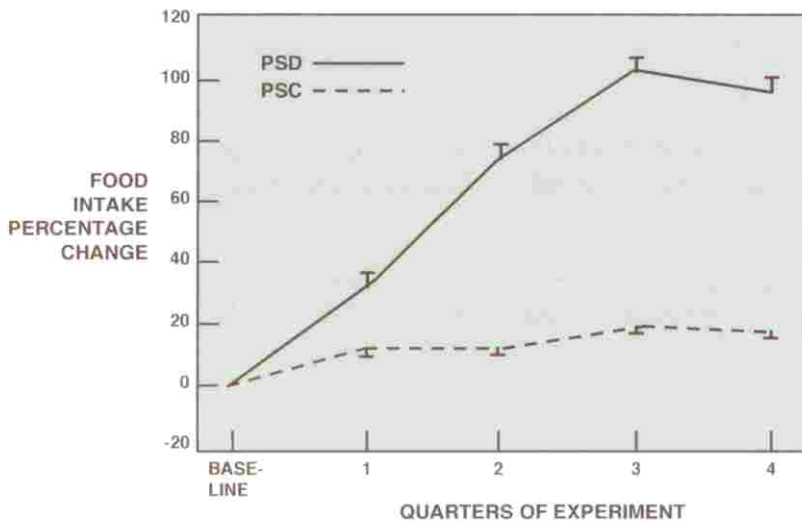


Fig. 11. Example of increased appetite.

This figure shows that cats ate almost twice as much during REM deprivation. They also ate much faster.

was an enhancement of the auditory recovery cycle in the cochlear nucleus in cats (14, 15).

SUMMARY OF RESULTS

The overall result of all these studies seemed to be that selective REM sleep deprivation increased brain excitability, which was, in turn, associated with intensification of certain behaviors. Other than its sheer difficulty, there were four reasons that we did not pursue the work into the 1970's: (*a*) none of our results suggested that REM deprivation is harmful, (*b*) very few methods were available to carry out further examination of the central nervous system, (*c*) the work was very labor-intensive and costly, and (*d*) the Stanford group had become interested in sleep disorders. Nonetheless, the changes we observed were so striking and so great, there must have been equally striking neurobiological-chemical-genetic changes.

Selective REM deprivation was carried out on the last cat for 69 consecutive 24-hour periods. This cat was, if anything, a stronger, healthier and better cat on REM-deprivation day 69 than when we started. Because of the lack of debilitating or fatal changes associated with REM deprivation (if anything, the changes were in the opposite direction), we finally concluded that a vital need for REM sleep does not exist in the adult organism (12). This left only the possibility that the vital function was performed in early development (31, see also 29).

Another reason, or rather a symbolic event, occurred at that time also. The notion that prolonged selective REM sleep deprivation might be associated with psychosis was not really disproven by the work in cats because there was a frequent eruption of REM sleep phasic events into the waking state, and in some of the human work we saw saw-tooth waves in the waking EEG. However, Dr. Gerald Vogel had started his studies of selective REM deprivation in schizophrenics and depressed patients. It was particularly noteworthy that he did not see a worsening of the psychotic state in schizophrenic patients as a result of selective REM deprivation (32). Sometime around 1969 I was visiting Allan Rechtschaffen's laboratory at the University of Chicago. He, Gerry and I went out to dinner. As we dined, I talked on and on about our REM deprivation studies when Allan finally erupted, "Dement, you'd REM-deprive your own mother." Almost in a heartbeat, Gerry Vogel said, "That's all right ... it wouldn't hurt her". And then they both laughed uproariously for what seemed about an hour – the symbolic end of my intense interest in selective REM deprivation.

The effect of selective REM deprivation has not been studied nearly as often in recent years. When I was carrying out REM deprivation studies, we had no method of quantifying daytime sleepiness, and had not demonstrated the cumulative daytime effect of partial sleep loss. In the interim, there has been only one study of selective REM deprivation utilizing daytime Multiple Sleep Latency Tests (27). This study found that selective REM deprivation does not increase daytime sleepiness compared to yoked controls.

As described in this paper, we did not obtain clear evidence of a vital function for REM sleep. Today, the mystery of REM sleep continues to elude solution. But as I said earlier, had we been more open-minded and not so focused on finding gold, I think there was lots of silver to be mined.

I will conclude my reminiscences by briefly contemplating Michel Jouvet's enormous contribution to the science of sleep. Where would we be had he continued to study conditioning rather than sleep? Who would have trained and inspired the countless basic sleep researchers that have followed in his path? His work and above all his presence have been of inestimable importance. It has been a great honor to participate in the 2003 Lyon Symposium and these proceedings which celebrate the career of a great scientist, an outstanding human being, and a dear friend.

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