

HOW SLEEP WAS DISSOCIATED INTO TWO STATES: TELENCEPHALIC AND RHOMBENCEPHALIC SLEEP?

M. JOUVET

Professor Emeritus Claude Bernard University

I was asked by many friends at the Symposium to write a brief history of my life and research until the beginning of the sixties. I expect that the young scientists (born after 1960) might be interested in the methods, tactics and strategy of neurophysiologists fifty years ago.

1. Some geographic and genetic backgrounds (1925-1945)

I was born in 1925 in Lons-le-Saunier, the "prefecture" of Jura, a country of mountains covered by large pine forests, at the border with Switzerland, in the east of France.

My father was a physician, but I was not interested in medicine and I wanted to be a naval officer.

In June 1940, Jura was occupied by the German army. After graduating from high school in 1942 I went to Lyons to study "special mathematics" necessary to enter the military Naval School. Unfortunately, in December 1942, most of the French Navy scuttled its own ships in Toulon and there was no hope for me to become a navy officer anymore. The life in Lyons, the capital of French resistance, occupied by German troops and special SS brigades and submitted to bombardment by the Royal Air Force was not a good place to aimlessly study mathematics! Thus, I went to the "Maquis" in the Jura mountains where I fought mainly against the so called "Vlassov Army". It was constituted of antistalinists soldiers made prisoners in Ukraine but the officers were German SS. They were very cruel and killed thousands of civilians and many of my fellows in the Maquis. After the liberation of Jura in August 1944, I volunteered in Alpine troops and went on patrol skiing across the Italian border during a terribly cold winter. In January 1945, our brigade was urgently dispatched along the Rhine River to defend Strasbourg which was attacked by German panzers. After May 1945, as a Sergeant, I went in occupation for two months in Vienna (Austria) and finally came back to civilian life in October 1945. At this time, I was still attracted by traveling overseas and decided to study anthropology and ethnography, but my father finally convinced me to enter the medical school in Lyons because "medicine can open almost every door". This is why I both entered the medical school and attended the lectures of Professor Leroy-Ghouran, a famous anthropologist who fortunately taught in Lyons at this time.

I embarked, at Le Havre, on the old *Georgic* that arrived in New York nine days later on a sunny morning of September 1954 which illuminated the statue of Liberty. I took the train in central station and arrived in Los Angeles after a wonderful five-day-trip.

3. *Magoun's Laboratory (September 1954-August 1955)*

The contrast between sunny, warm and rich Long Beach surrounded by its oil derricks and post war destroyed Lyons was as striking as was the discovery of Magoun's Laboratory. It was housed in wooden temporary buildings in the vicinity of the VA Hospital. At this time, the Brain Research Institute of UCLA was not yet built. It was just a project, a "dream" in Magoun's brain, who had to go almost every month to visit important administrative people in Washington. Magoun, who was a pupil of Ranson in Chicago, had recently moved to California and his work with G. Moruzzi (from Pisa, Italy) on the reticular formation had attracted many distinguished neurophysiologists (at this time, we did not use the terms "neurobiologists" or "neuroscientists"); J.D. French, the neurosurgeon of the V.A. Hospital who was lesioning the brain stem of Rhesus monkeys, John Green who had discovered the portal system in the pituitary stem, Eva King, who became Eva K. Killam, a pharmacologist, Robert Livingston, who came from Fulton's Laboratory, W. Ross Adey from Australia, Tom Sawyer a neuroendocrinologist who was working on rabbits and was of course considered eccentric by most people of the laboratory working either on Rhesus monkeys or in cats. (As far as I remember, nobody at this time was recording EEG in rats or in mice). There were also some foreign scientists.

Robert Naquet, from Marseille, had just left the laboratory when I arrived. He had taught the technique of "cerveau isolé" to Magoun, who called it the "Naquet isolé". C. Terzuolo, who had left Bremer's laboratory in Brussels, was also here, working on the effect of the vestibular system upon the spinal cord together with Bo Gernandt, a Swede. Finally, I came to share a small office with Professor T. Tokizane from Tokyo. I still remember very well the extraordinary patience of Pr. Tokizane who measured with a decimeter the intervals between units recorded from muscle spindles afferents. Every day, he used to draw by hand histograms from the kilometers of oscilloscope recordings on films that he was receiving from Tokyo. Finally, he obtained a two peaks histogram showing that there were two kinds of muscle spindles. He did in six months what a microcomputer could do now in a few minutes!

In 1954, every one of us was working on the reticular formation (anatomy of the ascending and descending pathways with Nauta's technique, pharmacology, stimulation, lesion, and it was the beginning of unit recordings).

All experiments were done on anesthetized cats with Nembutal or artificially ventilated under Flaxedil or D. Tubocurarin. However, I explained to H.W. Magoun, that I wanted to find some cortical EEG correlations by recording evoked potentials during Pavlovian conditioning in the cat. For this reason, I would have to develop a method to record chronically implanted cats.

minated in 1957 in Bremer's laboratory together with J.E. Desmedt (6).

Looking back through my notebook written during my stay in Long Beach, I found only two notes related to sleep or dreams. The first one was written in February 1955. I had followed the visit of a neurologist in the VA Hospital, and he showed me two observations of veterans from the Korean war with total transection of the spinal cord, who had "wet dreams" i.e. erotic dreams and ejaculation. We discussed the putative contribution of the sympathetic or parasympathetic system which could link the brain and the sacral nerves or the possibility of some "oneiric blood factor". This was my first encounter with the mysterious field of dreams ! The second note concerning sleep summarizes a discussion with Pr Sawyer who had just observed that, after coitus, a female rabbit would enter into a long arousal accompanied by the dropping of its ears (19). This was of course Paradoxical sleep, but none of us was aware of it. Any way, after fifty years, I still wonder at the exact mechanism of the "post coitus paradoxical sleep" and its putative function in a female rabbit.

Finally, at the end of my stay, I thought that my year in California has been very fruitful. I am still grateful to Pr Magoun and his associates for teaching me so many techniques and for the possibility to discuss with neurophysiologists from all over the world about the tactics and strategy useful for understanding the brain. When returning to France, I knew that I would have to develop the best method for chronic experiments and that a good strategy was probably better than very sophisticated apparatus. This was one of the best and happiest year of my life and I am glad to have the possibility to thank again my American colleagues for this "Californian dream".

4. My round the world trip during 3 months for 2700 \$

I left Los Angeles Airport on August 1st 1955 on a Pan-Am flight to Hawaii. I had read before a very useful popular book "How to travel without being rich" and organized my return trip so that I could visit the most interesting places with the less money. (At this time, some Airlines would pay your hotel even for a 6 days stopover, provided that you keep flying on the same Airline). For this reason, I bought a Pan-Am ticket Los Angeles-Singapore and made numerous stopovers in Hawaii, Canton Island, Fiji, New Zealand, Australia, and Philippines before arriving in Tokyo Haneda Airport where I met several students of Pr Tokizane. During my 15 days stay in Japan, I met Pr Matsumoto in Osaka who has read Pavlov (in Russian) when he was a war prisoner. He was interested in conditioning and came later in 1963 in my laboratory when he started to work with reserpine. This was the very beginning of the monoamines theory of sleep. In Osaka, I visited also Pr Yoshii who had discovered some sensory conditioning "the frequency specific response" i.e. when a cat is subjected to a 3 seconds bright light accompanied by intermittent auditory stimulations at 8-12-16-20 hertz, after many repetitions, the light alone would induce a similar rhythm on the auditory cortex. I was so puzzled by this experiment that I planned to study it in Lyons.

Experimental researches. I had to start the neurophysiological laboratory from almost nothing. By chance, I was visited by a USAF colonel, J.P. Henry. He was from the Air Office and Development Command in Brussels, and was visiting the few, West European neurophysiological laboratories where he could give some grant. J.P. Henry was a seasoned physiologist and I explain him the aim of my future research. Fortunately, I could obtained a grant of 2000 \$ a year, and the possibility to go by military air transport (MATS) to military airfield located on the east cost of USA for 1 \$.

Thank to this aid which continued up to 1962, I have been able to organize a small laboratory and to go to USA about 3 times a year.

Then I started to study the sensory conditioning and the "frequency specific responses" of Pr Yoshii.

I got more and more disappointed because the specific response had a frequency waxing and waning as cortical spindles. In fact, the cat became so drowsy during the association of light and tone that it was impossible to obtain a stable background of fast cortical activity. This kind of sleep was in fact looking like the "internal inhibition of Pavlov". Since according to Jasper, the spindle activity would be under the control of the intralaminar nuclei of the thalamus, I wrote a paper about the role of non specific thalamus in the "frequency specific conditioning response". This paper (one of the worst in my entire life) did not raise any question from the audience at the International Congress of Physiology in Brussels (1957) (8).

Since the occurrence of spontaneous sleep was an obstacle to sensory-conditioning, I decided to use sleep as a dependant variable. For this reason, at the end of 1957, I decided to study the mechanisms of habituation of cortical arousal in chronic cats. It was very easy to observe it: the first presentation of a tone in a sleeping cat would induce a cortical arousal lasting about 2-3 minutes whereas the fifth or sixth ones would not arouse any more the cat. Since we did not have a frequency analysis of slow wave, we had to find an index of "sleepiness" to deliver the tone at the same level of slow sleep. By chance, we recorded also from the ventral hippocampus and we found that during cortical slow waves, there would appear very high voltage "spikes" (more than 1 millivolt). Such activity had not yet been described and we spent two months to map out in acute experiment such activity which could be recorded under deep Nembutal. We found also that the inactivation of the cortex (by Novocain or refrigeration) would increase the spikes (14). For this reason we decided to use the hippocampal spikes as the signal to deliver the tone to the sleeping cat. This was easy because the voltage of the spikes were so big that the pens of the EEG machine did make a striking sharp and noisy click.

In order to disclose what were the structures involved in habituation (the "Pavlovian cortex" or the "Magounian reticular formation") we decided, together with François Michel, a young intern working with me, to study habituation either in chronic decorticated cats, or in cats with large lesion of the reticular formation, or in mesencephalic or pontine cats.

It took some time to keep chronic decorticated cats or mostly mesencephalic cat in good conditions and at a normal body temperature but we could not decide which

the pons) criteria, it was relatively easy to delimit the structures responsible for its triggering by local coagulation of the pontile reticular formation. Next, together with a young medical student, Daniele Mounier, who became my first wife in 1961, we observed that the lesions destroying the dorsolateral part of the pontine tegmentum could abolish selectively paradoxical sleep (PS) without altering SWS (15, 16). Unfortunately, at this time, there was not yet a histochemical map of the brainstem and the locus coeruleus was still a *terra incognita* on the stereotaxic atlases. Thus, the caudal part of N. reticularis pontis oralis and the rostral part of N. reticularis pontis caudalis were thought to be responsible for PS. There was nothing either in the histological aspect of these nuclei or in their projections which could give us some clue for understanding the mechanisms of PS or its functions. Apparently, this state of sleep was an active one, since we could trigger it by stimulating the pons during SWS. But the results of stimulation were rather capricious and we soon learned that PS could not be induced or lengthened at will, but that some "refractory period" existed after each episode. This leads us to speculate about some possible "neurohumoral" mechanism which would "discharge" periodically during sleep. Since atropine had a potent and selective suppressor effect, and eserine a facilitatory effect on PS, we speculated that cholinergic mechanisms were in some way implicated in PS.

Since PS still existed in pontile cats, it could be described as rhombencephalic sleep, whereas slow-wave sleep could be described as telencephalic sleep, since it was possible that it was related to the complex organization of the neocortex.

I published these results at the CIBA Symposium (1961) in London (17). I had a long discussion with N. Kleitman who presented the results of W.C. Dement. N. Kleitman thought that "activated sleep" was due to the basic rest activity cycle which was continuous during wake and sleep. With G. Moruzzi, who was interested in the insomniac midpontine preparation, we tried to rely both activated sleep and arousal, without success (1). Sir Adrian was chairman of the symposium. The only remark he made about sleep was that he thought that "his cat was sometimes snoring". Finally, the hypothesis that slow wave sleep depends upon the cortex and paradoxical sleep depends upon the rhombencephalic sleep is still valid to day. PS is also found in animals without eyes (as the mole) and in birds which do not move their eyes (the owl). This is why I still believe that the term of REM sleep is probably not the best to describe this strange state of sleep which function is still unknown.

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theory was right because even when the decorticated cats were behaviorally asleep, it was impossible to record spindles or slow wave in the thalamus or the reticular formation as in normal cats. However, there were still hippocampal spikes. For this reason, we made the hypothesis that the cortex (or the telencephalon) was responsible for the cortical and thalamo-mesencephalic slow wave activity of slow wave sleep but not for sleep since decorticated cats still presented the hippocampal spikes during very short behavioral sleep episodes, too short to study habituation (12).

As a next step we decided to record the muscular activity (EMG) to obtain some objective motor reaction which could habituate easily in mesencephalic cats. As any neurophysiologist knows, the easiest placement of EMG electrodes when implanting subcortical electrodes is the neck muscles because they are very close to the skull. Since we were operating on mesencephalic and pontile cats (from which we had removed all the neural structures in front of the pons), the only places to implant subcortical electrodes were the pons and, of course, the reticular formation. We were afraid that the implantation of electrodes in the medulla would be dangerous for these very fragile preparations. By chance, we implanted the electrodes in or very near the VI nerve nuclei (which is the best place to record PGO activity).

At first, we were very disappointed with our experiment. Even very loud auditory stimuli did not evoke much in the way of behavioral reactions in our chronic mesencephalic or pontile preparations, and it was almost impossible to record the EMG startle reaction because of the increase of muscle tone due to the decerebrate rigidity. However, during long-lasting EEG recordings (at this time only 3 to 6 hours) we were surprised to see, every 30 to 40 minutes, a periodic appearance of "spindle-like" activity in the pons, which coincided with the total disappearance of the EMG of the neck (which was normally much increase because of the decerebrate rigidity of our preparation). These curious episodes lasted about 6 minutes and occur periodically every 50 minutes (10, 12, 13). There were also movements of the vibrissae but we did not notice any eye movements which are almost absent during the first days after decerebration. We first thought that the "spindle like" activity (PGO activity occurs usually in bursts in mesencephalic cat) we had noted was an artifact of a central response evoked by the movements of the vibrissae, but fortunately the pontine phasic activity persisted after we had cut the vibrissae.

Apparently, then, we were faced with some kind of "hindbrain (rhombencephalic) sleep" which contrasted with slow-wave sleep (SWS). Very quickly we started similar polygraphic recording in normal cats. We were surprised to see that the cortical activity was similar to the cortical activity seen during waking at the time of total disappearance of EMG, but that the threshold for arousal was much increased. This was a paradoxical finding. At this time, W.C. Dement (1958) had just published his classical paper on "activated sleep" (2). It became evident that this "activated sleep" with rapid eye movements was in fact something very different from SWS, and that it was a different phase or state of sleep. To our surprise, we had to conclude that "dreaming" had to be triggered by a structure located in the lower brainstem.

Since "rhombencephalic or paradoxical sleep" could be recognized readily on behavioral (atonia and rapid eye movements) or EEG (spindle-like PGO activity in

I left Japan, for Hong Kong, Macao, Saigon and Singapore.

According to the popular book, I could theoretically go by train from Singapore to Europe, but there was still a war in Malaysia. For this reason I was obliged to stop in Kuala Lumpur and I spend 10 wonderful days in the paradise island of Penang where I could catch a plane to Bangkok. Then, I flew to Cambodia and Angkor, then Burma and Calcutta. In Calcutta, I took a train for Benares, Agra and Delhi. Later I could not arrive in Kashmir because the train was almost entirely flooded by a dramatic inundation in Penjab. Therefore I decided to go to Jaipur in the driest part of India. I visited Karachi, Beyrouth, Istanbul, Athenes and Rome. Then I took a train to Pisa where I visited Professor G. Moruzzi. He was very well informed about the researches going on in Magoun's laboratory. We discussed about the putative role of the reticular formation in the mechanisms of attention or conditioning. This was the first time I met this great physiologist who became a good friend until his death. Finally, I arrived in Lyons at the end of October. My 90 days trip has cost me exactly 2700 \$ (ie 10 \$ a day) including everything from plane tickets to souvenirs!

5. The research in Lyons (1956-1960)

Clinical research. I had to terminate my residency both in neurosurgery and neurology. In order to verify in man the subcortical control of visual inputs during attention or distraction I built a simple stereotaxic apparatus (9) which I used to record subcortical evoked visual responses to flash in the visual radiations. These recordings were made in conscious patients under local anesthesia at the time of ventriculography and I observed that the evoked potentials were bigger when the patients pay attention (in counting them) while they decreased if the patients made mental calculus (9). I did not continue these experiments for ethical reasons because of some unlikely lesioning of the occipital cortex.

At this time (1957-1959) I had also to take care of brain traumas, and many acute and chronic comatose patients. By recording the EEG and looking at their reactions to visual, auditory and painful stimuli I designed a very precise scale from full consciousness, to deep coma (11). Then I observed some patients (mostly young boys after motorcar accident) who has been tracheotomized and artificially ventilated. They had no reflexes, a full mydriasis, and their EEG was totally "flat". By using stereotaxy, I could not record any electrical activity in the thalamus, however, the heart rate and the blood pressure were normal but the central temperature decreased. Since I had seen many cases of irreversible flat EEG in cats artificially ventilated I knew it was impossible to resuscitate these patients who were in fact dead, because their brain was dead. I remember the difficulty I had to explain to the parents that their comatose child was dead even if we could hear the pulsations of the heart on the oscilloscope. This is why I published for the first time, the diagnostic of the death of the brain in 1959 (11).

