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THE DUALITY OF SLEEP REVEALED: THE HISTORY OF PARADOXICAL SLEEP

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INTRODUCTION

In the middle of the XXth century, at the time when EEG recordings, realized during the day, were short in duration, the EEG pattern of human sleep was considered to be well known in normal subjects as well as in patients. A "rapid" tracing becomes evidence of wakefulness, a "slow" tracing, of sleep.

The characteristics and the mechanism of this "sleep pattern" were considered as well understood, especially since experiments, realized in animals (the cat at this time) confirmed them. The interpretation of this results obtained had to be considered as limited due to the fact that they were realized in acute experiments and only based on cortical EEG records.

However, it seems necessary to recall some of these experiments:

- In the thirties, Bremer (2, 3, 4, 5) realizing different sections at the level of the brain stem, after "cerveau isolé préparation" whereas after "encéphale isolé" there was association of fast cortical activity (waking) and some spindles. Rheinberger and Jasper (27) and Hess *et al.* (11) considered slow cortical activity as the only EEG index of sleep in the non-anesthetized cat.
- In the forties, the demonstration of the role of thalamic nuclei in the induction of spindles (8, 9, 12) reinforced the importance of the thalamus in slow sleep.
- At the beginning of the fifties, the discovery that a specific electrical stimulation of the brain stem induces EEG fast rhythms and blocks spindles and slow waves, reinforced the notion that the reticular formation located in this region plays a fundamental role in "arousal" [Moruzzi and Magoun (26, 24, 25)].

All these experiments confirmed that low amplitude fast rhythms, accompanying "arousal" were replaced during sleep, following brain stem lesions or appropriate thalamic stimulation, by slow slow waves preceding or following spindles invading the cortex, the diencephalon and then the mesencephalic reticular formation.

However, rapidly some exceptions came to complicate this schematic vision of the sleep pattern (see Jouvet *et al.* 19, Jouvet 14).

- In the animal, midpontine pretrigeminal transection induces a marked predominance of behavioral and EEG signs of wakefulness (Batini *et al.*, 1) suggesting that structures lying between the midpontine section and the rostral end of the spinal cord might have a tonic synchronizing influence on EEG.

In chronic experiments, sectioning of the brain, between the quadrigeminal bodies, induces a cortical tracing which would lead, on EEG data, to the conclusion that the animal is asleep; in fact it reacts to pain by fleeing movements and miaowing (see Jouvet 14).

- In the animal as in man "synchronized" or "slow" tracing is not necessarily a sign of physiological sleep (barbiturate narcosis, some comas ...), as a "rapid" cortical activity is not necessarily a sign of wakefulness (ether narcosis ...).
- As early as 1938, Loomis *et al.* (23) described the existence of periods of rapid EEG cortical activity during sleep in normal subjects. This was confirmed latter by Rimbaud *et al.* (28) and by Roth (29) in some narcoleptic patients. Latter, the periodic recurrence of stage similar to descending stage one was observed every 90 minutes. This stage was accompanied by rapid eye movement and linked to dreaming. Thence it was christened it was "emerging one stage" by Dement and Kleitman (7); (see also Kleitman, 22).
- In the cat, the observation of "tiefer Schlag" ("deep sleep") with fast electrical activity by Klaue (21), was forgotten. Dement (6) described, in the cat, during behavioral sleep, the same occurrence of low voltage, fast EEG patterns accompanied by "absence of muscle potentials, relaxed posture, unresponsiveness and elevated auditory threshold". This EEG phase "was concomitant with many twitching movements of the limbs, vibrissae and ears". The technique used, did not permit Dement (6) to go further and for him, at this time, this phase was called "activated sleep".

THE EXPERIMENTAL RESULTS OF "THE JOUVET SCHOOL" AT THE END OF THE FIFTIES

Jouvet and his collaborators were interested in the putative role of the cortex or the reticular formation in the mechanism of habituation of "arousal" in the cat. During their observations of decorticate or decerebrate cats they discover (by serendipity: see Jouvet, this volume) the existence of a "state" without any activity in the neck muscles. Starting from these observations, the merit of Jouvet was to decide to conduct, with his collaborators, series of experiments, to try to understand the origin, the signification of this "periodic rapid sleep without EMG" and its relation with the "slow sleep". To study these two stages of sleep, in chronic cats, based on his intuition, knowledge and motivation, he chosen to continue to utilize the two different experimental techniques:

- Registration in association with the EEG of muscle activity (EMG), particularly the one of the neck muscles.

Effect of different types of brain sections or lesions

Animals were followed before or after decortication, sections ... realized under anesthesia. After surgical recuperation different parameters (EEG, EMG, EKG, respiration ...), were recorded continuously for long periods of time (see for details

Jouvet *et al.*, 1959; Jouvet, 1961). Reading forty years later, one is impress by the precision of the description of the characteristic signs of these two phases of sleep, even if some of them were not immediately clearly interpreted.

1) At first, the "Jouvet group" was devoted to describing with their own criteria the sleep organization in the normal chronic cat (Jouvet *et al.*, 1959). The two phases, very well known today, were carefully analyzed:

a) *Falling asleep and "slow" sleep*, is marked by the appearance of spindles followed by slow waves invading the cortex, the diencephalon, and then the mesencephalic reticular formation (R.F.).

The animal bends its head while the EMG of the neck muscles discreetly falls. Breathing is regular; the heart beat slows down; the threshold of arousal by direct excitation of the RF increases (20 to 50%).

b) *"Rapid" sleep phase or "paradoxical phase" (p.p.)*, always follows a "slow" phase and never appears immediately after wakefulness. It starts suddenly and is characterize by a rapid, low voltage EEG activity, identical to wakefulness, associate with slow rhythmic theta activity in the hippocampus, *commonly found during arousal:* (10) and at the pontile level with spindle bursts, (called later Pontogeniculo-occipital (PGO) waves (13). This phase, 10 to 15 minutes in duration, is periodically repeated (with an interval of 20 to 30 minutes) during behavioral sleep. EMG activity disappears totally in all muscles recorded. Eyeballs are frequently shaken by short rapid jerks in the vibrissae, the jaws and the tail. Breathing is irregular and superficial and the heart beat slowed down.

Auditory threshold is higher than during the slow phase as is the behavioral threshold of arousal through the direct FR stimulation (200 to 300%) than (Jouvet *et al.* 19; see also in Jouvet 14). Such signs supported the hypothesis that this phase is more profound than the slow phase.

2) This description of the two phases of sleep in normal cats was completed by the study of the effects of different brain lesions on sleep organization:

a) Partial decortication or total cerebellectomy do not modify the sleep organization [Jouvet and Michel (18)].

b) Total removal of the neocortex produces a permanent lack of spindles and slow waves for months (Jouvet and Michel, 16). Mesencephalic structures continuously exhibit a fast low voltage activity associated with all the other characteristics of the p.p.

c) In front of a section at the pontile or mesencephalic level, the cortical and diencephalic structures exhibit the EEG characteristics of the "cerveau isolé" (Bremer, 2), whatever the state of the animal.

Behind the section, if mesencephalic activity remains rapid during waking, during p.p. spindles (*the future PGO waves*) appears at the pontile R.F., EMG activity disappears in the neck muscles and respiratory and EKG are modified.

Intervals between two p.p. are longer than in intact animals.

d) Section at the level of the posterior part of the pons does not induce the modifications observed in mesencephalic or pontile animals during p.p. In front of the section EEG activity resembles that described by Batini *et al.* (1).

THE "JOUVET SCHOOL" IMPACT ON THE KNOWLEDGE OF THE PARADOXICAL SLEEP

If the two phases of sleep were almost described by Dement and Jouvet, the second was the first to clearly demonstrate the origin of each one and particularly of the p.p.

The "slow sleep" characterized by spindles and slow waves require the presence of neocortex and thalamic structures. It was described as "telencephalic sleep".

The "rapid sleep" phase or "paradoxical phase" depends on the system (*"circuits" will be now preferable*), situated at the level of the pontile RF: Its control through the inhibitory reticular formation, the somato-vegetative phenomena (disappearance of all muscular tonic activity, variation in respiratory and cardiac rhythms ...). The rapid cortical activity which accompanies this phase is not suppressed by the interruption of the activating reticular system. " This phase which only exists in mesencephalic and pontile cats could be likened to an "archisleep". For all these reasons Jouvet (14) called the "rapid sleep phase": the"rhombencephalic phase" (*In fact it was the birth of the "Paradoxical Sleep", its actual name*).

During this period, the experiments realized by Jouvet, do not stop with this definition!

One may quote:

- The confirmation of the results of Dement and Kleitman (7) and the addition of new arguments as the description of saw tooth waves during REM sleep (Jouvet *et al.* 20; see also Jouvet and Jouvet 15) showing the relation between p.p. and the oneiric activity in man.
- The utilization of a pharmacological approach to complete his p.p. knowledge [Jouvet and Michel (18)]. He demonstrated that if atropine considerably reduces the duration of p.p., the injection of eserine produces longer p.p. although their frequency was not increased. These first pharmacological data were a puzzle to him. In 1961, he did not hesitate to write: "this facts are difficult to explain as a whole through purely neuronal mechanisms", and also "it is suggested that this phase depends upon neurohumoral mechanism". He was just utilizing a new conception of the physiology where the "neurophysiologie humide", becomes a complement of the "neurophysiologie sèche" (*this new concept will become the basis of the "Neurosciences" ten years later*).

CONCLUSIONS

The results obtained by Jouvet and his group enable them to dissociate the two phases of sleep, which were considered as independent of one another: Decortication or mesencephalic lesions induces the disappearance of "slow" sleep, but permit the persistence of "paradoxical sleep". Pontile lesion induce the disappearance of "paradoxical sleep", but permits the persistence of "slow sleep". The full independence of this two stages were later on considered to be too schematic by

some authors, but " the intervention of the two different systems during physiological sleep in the cat" (Jouvet, 14) stays more than forty years later a landmark in the history of sleep study. The existence of these two phases of sleep and the importance of one in relation to the other, became a way to study, with different approaches (from neurophysiology to neurochemistry, genetic ...), the physiology of brain functioning and its variation depending of the phylogenesis, the ontogenesis and the pathology.

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