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OBITUARY

In Memoriam: Michel Jouvet (1925–2017)

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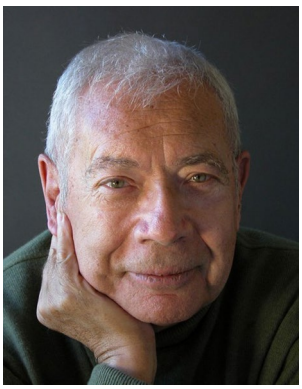

Professor Michel Jouvet, pioneer and unchallenged leader in the field of sleep research, passed away at Villeurbanne (France) on October 3rd, 2017 at the age of 91. Sleep research has lost a renowned hypnologist, a tremendous and endearing mentor, recognized and respected worldwide. He was married to Dr. Anne Jouvet and had four children. His most remarkable discoveries reside in the definition of the electroencephalographic (EEG) characteristics of brain death (irreversible coma), and the identification of the third state of the brain, i.e., "Paradoxical Sleep".

1 Prior to research activities

Michel Jouvet was born on November 16th, 1925 at Lons-le-Saunier (Jura, France). Since he was 10 years, his father, a medical doctor, encouraged scientific games. Michel Jouvet attended the "Rouget de l'Isle" secondary school at Lons-le-Saunier. Initially, he wished to become a sailor. However, during the second world war, the French Fleet scuttled in the harbor of Toulon, which cooled off his dreams. He joined the underground in Jura, the Alps, Alsace, and was incorporated as a sergeant in the French First Army. After the Liberation, he was promoted as Alpine sergeant. He received "la Croix du combattant volontaire de 1939–1945" and the "Légion d'honneur".

2 Medical and scientific training

Back to civil life, he chose to follow medical training at the Faculty of Medicine of Lyon and became a medical doctor of the Faculty of Medicine of Paris in 1956. He was also attracted by ethnology and obtained a degree in this discipline. He then specialized in neurobiology, neurosurgery, and neuropsychiatry. Michel Jouvet himself said that his final decision to run in the brain physiology came from the training that he had in neurosurgery, the great misery of the patients that he had to care and the poor knowledge of the brain functioning.

3 Research path

In 1954, while in an internship, Michel Jouvet received a Fulbright grant and joined Professor Horace Magoun's laboratory at Long Beach Veteran's Hospital (California).

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In this laboratory, he became familiar with anatomical techniques (Prof. Walle J.H. Nauta) applied to the ascending and descending pathways of the reticular formation. To achieve long-term chronic recordings of evoked potentials in relation with Pavlov conditioning, Michel Jouvet developed a technique of chronic electrode implantation. Data obtained with this approach have been at the basis of the first scientific paper published by Michel Jouvet and co-signed by prof. Horace Magoun.

At Long Beach, Michel Jouvet met with most famous scientists of the 20th century such as Giuseppe Moruzzi, Robert Naquet, Herbert Jasper, and Raul Hernandez-Peon. It is also there, in 1955, that Michel Jouvet began to question himself about dreams. Such a questioning concerned soldiers of the Korean war and the sleep behavior of rabbits after coitus.

Back in France in October 1955, Michel Jouvet conducted research constantly fruitful. His main discoveries can be summarized as follows.

He began the study of comatose patients bearing cerebral lesions. Using electroencephalographic recordings and the ability of patients to react to visual, hearing or painful stimuli, Michel Jouvet defined a very precise scale running from a fully active conscience to a state of nonresponsiveness to the stimuli, i.e., profound coma. In the latter condition, the electroencephalographic activity is completely "flat" (cortical and subcortical structures) testifying brain death and irreversible coma. The classification was fully recognized afterward and it is still currently employed by neurologists.

In 1959, Michel Jouvet noticed that slow-wave sleep, in both animals (cats) and humans, preserves a slight muscular activity. This activity, however, was sometimes followed by a state of the brain close to that of the waking state remarkably accompanied by a drop in neck muscles tone. Such a paradoxical atonia drove Michel Jouvet to define a third state of the brain that was called "paradoxical sleep". In parallel, this state was named rapid eye movement sleep (REM sleep) by William C. Dement and the American school.

In 1961, Michel Jouvet classified two different sleep states: telencephalic sleep, according to the slow waves characterizing the EEG recordings; rhombencephalic (paradoxical) sleep, according to the fast waves of the EEG, the atonia of the muscles, and the presence of rapid eye movements concomitant with intracerebral ponto-geniculo-occipital (PGO) waves close to VIth nerve nucleus. Afterwards, the dependence of paradoxical sleep from the pontine structures was demonstrated using the pontine cat preparation (removal of part of the brain anterior to the pons) and electrocoagulation of structures of the dorsal pontine tegmentum. The latter experiments, triggering a complete disappearance of paradoxical sleep, while slow-wave sleep was maintained, were achieved by Danielle Mounier (Michel Jouvet's first wife). Here, we want to point out that, constantly, Michel Jouvet defended the terminology "paradoxical sleep" versus "REM sleep", because this state of sleep is still present in pontine cat preparations, and exists in animals with poor eye movements (bird) or limited eyeballs (mole).

The hypothesis arguing that close relationships do exist between dreaming and the occurrence of paradoxical sleep was developed in Lyon and also in California (Prof. William Dement). Subjects awakened during paradoxical sleep were capable to describe clear and well-constructed oneiric memories (> 80%), while subjects awakened during slow-wave sleep had only poor oneiric memories (< 7%). Beside, Michel Jouvet demonstrated that homeotherms, particularly the cat, where capable to exhibit oneiric behaviors when a lesion of the locus coeruleus alpha, an area responsible for paradoxical sleep atonia, was performed. The cat seemed to live its dreams, playing with a mouse or being afraid of some ghost. It was thus suggested that homeotherms, whether being animals or humans, do dream.

Studies relative to phylogeny and ontogeny of sleep were also achieved. Fishes, amphibians, and reptiles exhibit a rest–activity cycle, but these species do not express behavioral or electroencephalographic signs of paradoxical sleep. It is peculiar that these poikilotherms do not possess an active regulation of their body temperature. Nowadays, it is established that the occurrence of paradoxical sleep is concomitant with the installation of the homeothermy. Thermoregulation takes place despite its important energetic cost. As an example, the occurrence of paradoxical sleep requires about five times more ATP than during the waking state. One may consider that if phylogeny led to the apparition of paradoxical sleep despite its high energy cost, it may be because its function is essential.

Throughout the ontogenetic approach, conducted in parallel with phylogenetic studies, high amounts of paradoxical sleep were described in newborn homeotherms and in utero fetuses. Again, such information pointed out the crucial role of this state of sleep in the somatic and neuronal development of homoeothermic species.

Together with the above approaches, active pharmacological, electrophysiological, and anatomical studies were also conducted. The particular place of serotonin in sleep preparation was documented. Multiple neuronal networks involved in sleep production were identified by combining polygraphy, single unit recording, and marking of anatomical pathways. At the beginning of these studies, pathways of brain PGO waves were described in the cat. Their genesis in specific structures of the dorsal pontine tegmentum and their relationship with the peripheral rapid eye movement were established (a central PGO wave is constantly followed by a peripheral rapid eye movement). The PGO waves significance, however, still remains an enigma. These waves might be involved at first in brain plasticity, since disruption of

their pathways, from the pons to the visual system, impoverishes the density of the synapses. The PGO waves might also be involved in the triggering of the oneiric imagery that takes place during paradoxical sleep, its softness, its strangeness, or its violence. These aspects remain to be further investigated.

Throughout his entire career, Michel Jouvet never forgot the fertile animal/human interface and conducted studies in parallel in animals and humans. In this respect, the discovery of modafinil, a molecule sustaining a long-term calm wake in the cat, appeared to be very efficient in human to treat idiopathic hypersomnia and narcolepsy (even in children). This molecule is now also employed by the military for the maintenance of a high level of vigilance and performance of soldiers in continuous or sustained operations.

Since his initial questioning about dreams and their significance at Magoun's Long Beach Laboratory (1955), Michel Jouvet remained highly interested in this aspect. He collected several thousand dreams recalls and he introduced scientifically a dependence of the dream contents to the dreamer's environment. Dreams appear to be time locked with external events. This relationship predominates when considering the days preceding the dream, but, afterward, it wanes rapidly.

Michel Jouvet also issued his theory on the iterative programming that occurs during paradoxical sleep in homeotherms. Such a programming would aim at covering the poor neurogenesis of homeotherms (contrarily to that of poikilotherms), to maintain the specific behaviors of the individual.

In conclusion, Michel Jouvet was undoubtedly one of the major actors and thinkers who developed the sleep discipline. He contributed markedly to create a worldwide Sleep School that will lead new generations of scientists for many decades. We are proud to have been his disciples.

4 Major awards

(1) Prix Laborde de la Société de biologie (1961); (2) Prix Bing de l'Académie des sciences médicales de Suisse (1966); (3) Intra Science Awards, Los Angeles (1981); (4) Prix de la Fondation pour la recherche médicale (1983); (5) Médaille d'or Morgani, université de Padoue (1988); (6) Médaille d'or du CNRS (1989); (7) Distinguished Scientist Awards of the Sleep Research Society, Etats-Unis (1989); (8) Prix mondial Simone et Cino del Duca (1991); (9) Prix recherche et médecine de l'Institut des sciences de la santé (1991); (10) Prix Blaise-Pascal (1991); (11) Prix Maurice-Pérouse de la Fondation de France (1993); (12) Prix international Fyssen (1997); (13) Prix Farell Sleep Medicine, Harvard Medical School, USA (2003); (14) Docteur honoris causa des universités de Zurich, Suisse (1986), d'Haifa, lsraël (1991), de Liège, Belgique (1992) et de Montréal, Canada (1993); (15) Officier de la Légion d'honneur, commandeur dans l'Ordre national du mérite, commandeur des Palmes académiques, officier dans l'Ordre du Mérite du Niger; and (16) Croix du combattant volontaire 1939–1945.

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(4) *Le château des songes*, Paris, Odile Jacob, 1992.
(5) *Le Grenier des rêves*, Paris, Odile Jacob, 1997.
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(7) *Le voleur de songes*, Paris, Odile Jacob, 2004.
(8) *De la science et des rêves*: *mémoires d'un onirologue*, Paris, Odile Jacob, 2013.
(9) *Le sommeil, la conscience et l'éveil*, Paris, Odile Jacob, 2016.