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MICHEL JOUVET: A PERSONAL TRIBUTE

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This personal tribute to my mentor, Michel Jouvet, is meant to emphasize the way in which his daring, dashing personal style and his cultural background contributed to his scientific achievements. My main contention is that Michel Jouvet was not afraid, indeed he was proud, to place his synthetic intelligence above his analytic capabilities. In this way, he worked in the tradition of his great French physiologist predecessor, Claude Bernard, for whom it was always the integrative idea that guided scientific inquiry.

Some of the subthemes of this essay concern specific hypotheses boldly put forward by Michel Jouvet concerning not only the mechanism but also the function of REM sleep. I will discuss three Jouvet hypotheses:

1. The limbic midbrain pathway is the route of cortical activation in REM sleep (as against the traditional midbrain reticulo-thalamic pathway which activates the cortex in waking). This was the hypothesis that I was set to test during my training year in Lyon, 1963-64.
2. The biogenic amine neurones constitute a brain stem lobby for the control of waking (dopamine), slow wave sleep (serotonin) and REM sleep (norepinephrine). This hypothesis emerged during my stay in Lyon and became the major organizing concept of my single cell recording studies undertaken in collaboration with Robert McCarley from 1968-1984.
3. REM sleep is an internal activation program designed to develop and maintain such instinctual behavior patterns as fright, flight and fight on the defensive side, find-a-mate, fornicate, and fecundate on the more creative side. This idea was honed and advanced in recent years but had its origins in the discovery of REM sleep without atonia which was made when I was in the Lyon Laboratory.

Before discussing these three hypotheses, it is important to sketch, in what I hope is a dispassionate way, the differences in scientific philosophy that I brought to my encounter with Michel Jouvet. At the Harvard Medical School in Boston and at the National Institutes of Health in Bethesda, Maryland, I had been encouraged to be skeptical, tough-minded, and quantitative. Scientific hypotheses were meant to be shot down, and scientific logic was meant to be questioned.

When I discussed going to Lyon with my colleague, Eric Kandel, he cautioned me about the lack of scientific rigor in sleep research. I had previously gone with Eric and Peter Huttenlocher to a presentation at the Massachusetts General Hospital by Giuseppe Moruzzi of his work in the mediopontine transected cat (12). This was

Moruzzi's Harvey Lecture. I found it difficult to understand and I was not then able to tear it to shreds as Eric and Peter did. "Neurophilosophy" was their damning epithet because the work did not take cellular and molecular mechanisms into account as they thought neurobiological science should.

Ed Evarts, who was one of my mentors at the NIMH, said he knew what Eric meant but thought the work was sound and interesting anyway. Ed, like Michel Jouvet, had worked with Horace Magoun at UCLA. Magoun was, of course, Moruzzi's collaborator in the work that led to the reticular activity system concept. My other NIMH mentor, Fred Snyder, was more enthusiastic about the chance to work with Jouvet. We had both read Jouvet's epochal 1962 paper on the pontine brain stem mechanisms of REM sleep generation (7).

On the strength of these opinions, I arranged to have Jouvet invited to give a seminar at the NIH. If you have ever heard him speak, you will understand why I was so excited by the prospect of going to Lyon. I picked up Michel at Union Station and during the drive out to Bethesda we negotiated the terms of my fellowship. I was to find the money and he was to speak only French to me. I would have a project to pursue independently with his supervision. All of those terms were easily met and I had a wonderful year.

But it would be a mistake and an important point would be missed if I failed to mention that my relationship with my mentor was filled with tension. Most of that tension was stylistic and had to do with the inevitable clash between the synthetic and the analytic paradigms. In the balance of this paper, I hope to show that creative compromise – and the passage of time – has resolved most of these issues. In keeping with the spirit of tribute, I will emphasize the general point that in most of his synthetic ideas, Michel Jouvet was ahead of his time. His ideas were also beyond the power of the methods he used to test his ideas analytically.

1. THE LIMBIC MIDBRAIN CIRCUIT CAUSES REM SLEEP CORTICAL ACTIVATION

This was one of the cardinal hypotheses put forward in Jouvet's 1962 paper that had impressed me so much (7). The scientific origin of the idea was Walle Nauta's (13) description of the circuit and Jouvet's recognition that there had to be some important differences between the mechanisms of cortical activation in REM sleep and waking. After all, sleep persisted in the face of this powerful activation; maybe that meant a different brain mechanism was involved. And, of course, there were those dramatic differences between the mental states associated with the activation: for Jouvet, dream consciousness was much more emotional than waking (and hence more limbic).

Now that we know from PET studies that there is selective activation of the limbic forebrain, we see how right Michel Jouvet's synthetic hypothesis really was. The mechanisms and the phenomenology *are* different in now more easily understandable ways (1, 10, 14).

But in 1963, we didn't have these methods. We had only Radio Frequency lesions, ablations, transections and electrical stimulation techniques to work with. So I fried, cut and buzzed the brainstem in a vain effort to prove my mentor correct. It didn't work. Short of total transection and/or forebrain ablation, no matter what we did to those poor cats, they managed to activate their forebrains in REM sleep. Whether the lesions and transections were dorsal or ventral, whether they destroyed the midbrain or the hypothalamus, cortical activation remained robust in REM sleep. I was forced to conclude, rather sadly, that my experiments provided no evidence for the limbic midbrain circuit hypothesis and that REM sleep cortical activation depended upon an intact reticulo-thalamic activating system (5).

With respect to my research, I felt a bit deceived and a bit of a failure. But I learned so much from Jouvet that year that I returned to Harvard determined to apply the techniques of another mentor, the single cell recording method of Ed Evarts (3), to the problem of Jouvet – how does the pons generate REM sleep.

As I was doing my work in Lyon, I often visited Jouvet whose office and lab were across the hall. Jouvet was a skillful neurosurgeon and made pontine cats with great deftness and skill. The pontine cat with all of its forebrain (plus of minus the hypothalamus) in the suction bottle under the operating table still evinced periodic muscle inhibition. "There must be a cellular clock in the pons", I said, trying in vain to convince my Gallic colleague to use the single cell approach to analysis of the mechanism. "Anglo-Saxon heresy" was his phrase in discussing John Eccles' book "The Physiology of Nerve Cells" when it arrived by mail.

Cellular neurophysiology was thus associated with the English who were also called "Les Ennemis Hereditaires", (referring to centuries of conflict) and "perfidious Albion" (referring to the sinking of the French fleet in Toulon during World War II). Cellular neurophysiology was also taboo because it was practiced in Paris, by the Fessards, who exercised enormous power over the science done in places like Lyon. I was astounded to realize how deep these feelings were. As an admirer of both England and France, I was immediately placed in conflict and in jeopardy.

It took me longer than I care to admit to realize what was going on. "No Englishman would ever make such disparaging remarks about the French", I asserted. But when I was paid a surprise visit by a schoolmate friend from a previous year spent in England, I was amazed at the stream of anti-French invective that sprung spontaneously from his mouth.

One night in Jouvet's apartment, I made the mistake of saying that the Vin Jaune that he so proudly served tasted like sherry. For Jouvet, the vin jaune was as French as Charles de Gaulle and could therefore have nothing English about it. But it *did* taste like sherry. This was probably because the yellow color was a result of normal maderisation of the wine.

I thank Jouvet for introducing me, in such a passionate and vivid way, to the problem that my work would focus on for the next 16 years. As Jouvet and Kazuo Sakai were also soon aware, cellular neurophysiology had much to offer sleep research whether it was Anglo-Saxon heresy or not!

II. THE BRAINSTEM'S BIOGENIC AMINE LOBBY

I was in the Jouvet Laboratory when Michel read of the Swedish neuroanatomy papers describing the biogenic amine neurones of the pons and midbrain (2). With characteristic opportunism and experimental adventurousness, Michel Jouvet quickly used the new neurobiology to formulate a new theory of sleep-wake state control. If I am not mistaken, the first experiments, using reserpine to deplete the amines, were done by Jungi Matsumoto, a visiting scientist from Japan who taught me the art of haiku poetry at the same time that we worked on the brainstem mechanisms of sleep.

It was not long before Jouvet had amassed abundant raphe-lesion and pharmacological evidence for a positive role of serotonin in slow wave sleep generation (8). Less strong evidence prompted him to propose that the locus coeruleus norepinephrine system generates REM and that the dopamine system was responsible for waking. All very neat but mostly wrong as the single cell studies that were branded as Anglo-Saxon heresy revealed. Somehow, Jouvet's earlier REM sleep generator molecule, acetylcholine, got lost in the shuffle.

I remember the crisis that occurred when Jouvet challenged the data favoring acetylcholine presented by his former colleague, the Mexican scientist, Raul Hernandez-Peon. Hernandez-Peon was so upset that he walked out of the session and did not appear again at that meeting. It is ironic that Jouvet was correct in his initial proposal that cholinergic mechanisms were important in REM generation. So was Hernandez-Peon although his evidence was rather weak (4). It turned out that the biogenic amine lobby of the pons was involved, along with dopamine, in wake state generation both the serotonin and norepinephrine neurones decreased their firing – and their neuromodulatory output – by almost 50% in slow wave sleep and almost 100% in REM. (6)

In this case, Michel Jouvet was right in his broad hypothesis – and wrong in many of its details. But the important point is that he shaped the agenda for the neurobiology of sleep for twenty years. And he has recently had the grace to admit his mistakes even if he still grasps at serotonin straws whenever they blow his way.

As mentioned above, Jouvet is also to be credited for his support of Kazuo Sakai whose work helped to overturn Jouvet's biogenic amine hypothesis of the late sixties. This work is as meticulous and analytical as anything done by us Anglo-Saxon heretics and – by and large – fits with the picture suggested by the reciprocal interaction model that Robert McCarley and I formulated (11). We would never have formulated that model without Michel Jouvet's influence.

III. DREAMING AND THE FUNCTION OF REM SLEEP

Does everyone know that the youthful Michel Jouvet was an amateur artist whose macabre ink drawings were inspired by Andre Breton, the intellectual father of French surrealism? I saw these drawings on the same night as the Vin Jaune imbroglio.

My point here is that Michel Jouvet was as excited as any of us by the prospect of explaining dreaming physiologically. He was therefore as ready as Bill Dement, Fred Snyder, and the rest of us to equate dreaming and REM. That was a mistake we all made together. When it was shown, without doubt, that dreaming could occur at sleep onset and in late night NREM sleep it tended to take the wind out of our collective sails.

But, at the risk of another Anglo-Saxon heresy, let me assure everyone, Michel Jouvet including, that the association of dreaming and REM physiology is robust if we take a more global, statistical, and state space approach to the psychophysiology. Dreaming is associated with activation (A), with the closing of input-output gates (I), and with decreased 5-HT, NE/Ach ratios (M). REM sleep is the brain state characterized by the greatest contrast of A, I and M from waking but there are other states of the brain where these values are strong enough to support dreaming.

Jouvet was never foolish enough to propose that the function of REM sleep was dreaming as many other post-Freudians did. But I think he was the first to suggest that REM allowed the sleeping brain to run a variety of instinctual programs like fear, flight, fight, find-a-mate, fornicate, and to fecundate, an idea that still has as much appeal despite the paucity of empirical support (9).

I, for one, like Jouvet's behavioral rehearsal hypothesis. It is a post-Freudian idea in the best sense of the word. And it well fulfills the subtitle of this meeting, the unfinished story of REM sleep. However this story turns out, and however other important stories turn out, the name of Michel Jouvet will always be remembered. How lucky we all are to have known him!

REFERENCES

1. Braun, A.R., Balkin, T.J., Wesenten, N.J., Carson, R.E., Varga, M., Baldwin, P., Selbie, S., Belenky, G., and Herscovitch, P. Regional cerebral blood flow throughout the sleep-wake cycle. An H2(15)O PET study. *Brain*, **120:** 1173-1197, 1997.
2. Dahlstrom, A., and Fuxe, K. Localization of monoamines in the lower brain stem. *Experientia*, **20:** 398-399, 1964.
3. Evarts, E.V. Activity of neurons in visual cortex of the cat during sleep with low voltage fast EEG activity. *J. Neurophysiol.*, **25:** 812-816, 1962.
4. Hernandez-Peon, A., Chavez-Zbarra, G., Morgans, P.J., and Timo-Iaria, C. Cholinergic pathways involved in sleep and emotional behavior. *Exp. Neurol.*, **8:** 93-111, 1963.
5. Hobson, J.A. L'Activité electrique phasique du cortex et du thalamus au cours du sommeil desynchronisé chez le chat. *C. R. Soc. Biol. Paris*, **158:** 2131-2135, 1964.
6. Hobson, J.A., McCarley, R.W., and Wyzinski, P.W. Sleep cycle oscillation: reciprocal discharge by two brain stem neuronal groups. *Science*, **189:** 55-58, 1975.
7. Jouvet, M. Recherches sur les structures nerveuses et les mecanismes responsables des differentes phases du sommeil physiologique. *Archives Italiennes de Biologie*, **100:** 125-206, 1962.
8. Jouvet, M. Biogenic amines and the states of sleep. *Science*, **163:** 32-41, 1969.
9. Jouvet, M. Essai sur le revu. *Archives Italiennes de Biologie*, **111:** 564-576, 1973.

10. MAQUET, P. Functional neuroimaging of sleep by positron emission tomography. *J. Sleep Res.*, **9:** 207-231, 2000.
11. MCCARLEY, R.W. AND HOBSON, J.A. Neuronal excitability modulation over the sleep cycle: a structural and mathematical model. *Science*, **189:** 58-60, 1975.
12. MORUZZI, G. Active processes in the brain stem during sleep. *Harvey Lect.*, **58:** 233-297, 1963.
13. NAUTA, W.J.H. Hypothalamic regulation of sleep in rats. An experimental study. *J. Neurophysiol.*, **9:** 285-316, 1946.
14. NOFZINGER, E.A., MINTUN, M.A., WISEMAN, M., KUPFER, D.J., AND MOORE, R.Y. Forebrain activation in REM sleep: an FDG PET study. *Brain Res.*, **770:** 192-201, 1997.