CC/NUMBER 17
APRIL 25, 1983

This Week's Citation Classic

Jouvet M. Biogenic amines and the states of sleep. *Science* **163**:32-41, 1969.
[Department of Experimental Medicine, School of Medicine, Lyon, France]

The inhibition of the biosynthesis of 5-hydroxytryptamine (5 HT) by *p*-chlorophenylalanine is followed by a total insomnia which can be reversed into physiological sleep by a secondary injection of 5-hydroxytryptophan, the direct precursor of 5 HT. The destruction of 5 HT-containing neurons of the raphe system is also followed by the suppression of sleep. These results suggest a relationship between brain 5 HT and sleep. [The *SCI*® indicates that this paper has been cited in over 690 publications since 1969.]

M. Jouvet
Department of Experimental Medicine
Claude Bernard University
69373 Lyon
France

February 11, 1983

"When this paper was published in the first issue of *Science* for 1969, there was an explosive growth of sleep research which was due to the changes of the paradigm concerning the mechanisms of sleep. It has been admitted only recently that sleep is an active phenomenon, which contradicts the long held belief that sleep is a passive state of the waking system. Moreover, two different states alternating periodically during behavioural sleep had been discovered about ten years before —slow-wave sleep (SWS) and paradoxical sleep (PS) or REM sleep.[1] At first, the sleep mechanisms were studied with the so-called 'dry neurophysiology' (microelectrode recordings, stimulation, etc.). However, the time constant of the rebound of PS which may last for weeks could not be explained by classical synaptic physiology. It was then time for pharmacology.

"A first step in the direction of monoamines had been taken in 1964 by Jungi Matsumoto from Tokushima in my laboratory in the department of experimental medicine in Lyon. He demonstrated that after pretreatment with reserpine, a monoamine depletor drug, 5-hydroxytryptophan (5 HTP) or dopa could restore SWS and PS respectively.[2] In 1966, thanks to Weissman's courtesy, I obtained a small amount of p-chlorophenylalanine. This drug was most interesting since it could suppress the biosynthesis of serotonin (5 HT) by inhibiting tryptophan hydroxylase[3] and induce a total insomnia. However, secondary injection of 5 HTP could still restore 5 HT and sleep.

"At about that time, the pharmacology of monoamines acquired some anatomical dimension thanks to histofluorescence and the mapping of monoaminergic neurones by Dahlström and Fuxe.[4] Thus, it became possible to directly attack 5 HT neurons by lesion of the entire raphe system. These lesions could suppress SWS or PS and biochemically decrease 5 HT in the brain. This was the ground for the monoaminergic theory of sleep which was first described in this paper and was further developed in a long paper in 1972.[5] At first, this theory could predict the effect of drugs acting upon monoamines in the sleep-waking cycle. However, since that time, some new experimental evidence seems to contradict the hypothesis that 5 HT is a sleep neurotransmitter. On the contrary, 5 HT neurons are more active during waking than during sleep and 5 HT release is increased during waking. These findings led to the hypothesis that during waking, 5 HT could act both as a transmitter and a neurohormone in inducing the synthesis and/or the liberation of some sleep factors). This hypothesis —and the discovery of numerous putative sleep factors —returns the sleep mechanism back to Pieron sleep hypnotoxin.

"I think that this paper has been cited so often for several reasons. First, it was one of the first reviews describing in detail PS and its ontogeny and phylogeny. Secondly, the states of sleep were described in quantitative terms which could be used as dependent variables for any pharmacological or surgical interventions. Thirdly, multidisciplinary approaches (polygraphic, pharmacological, biochemical, histochemical) were followed in altering 5 HT metabolism and quantitative data could correlate the amount of alteration of a biochemical system in the brain with a physiological state."

1. **Jonvet M**. Recherches sur les structures nerveuses et les mécanismes responsables des différentes phases du sommeil physiologique. *Arch. Ital. Biol.* **100**:125-206, 1962.
2. **Matsumoto J & Jouvet M.** Effets de réserpine, DOPA et 5 HTP sur les deux états de sommeil. *C.R. Soc. Biol.* **158**:2137-40, 1964.
[The *SCI* indicates that this paper has been cited in over 80 publications since 1964.]
3. **Koe B K & Weissman A.** p-Chlorophenylalanine, a specific depletor of brain serotonin. *J. Pharmacol. Exp. Ther.* **154**:499-516, 1966.
[The *SCI* indicates that this paper has been cited in over 1,270 publications since 1966.]
4. **Dahlström A & Fuxe K.** Evidence for the existence of monoamine-containing neurons in the central nervous system. 1. Demonstration of monoamines in the cell bodies of brain stem neurons. *Acta Physiol. Scand.* **62**(SuppI. 232):5-55, 1964.
5. **Jouvet M.** The role of monoamine and acetylcholine-containing neurons in the regulation of the sleep-waking cycles. *Ergebnisse Physiol.* **64**:166-307, 1972.
[The *SCI* indicates that this paper has been cited in over 490 publications since 1972.]