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Author manuscript

*Arch Ital Biol.* Author manuscript; available in PMC 2022 May 30.

Published in final edited form as:

*Arch Ital Biol.* 2001 February ; 139(1-2): 3–10.

## A TRIBUTE TO NATHANIEL KLEITMAN

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Nathaniel Kleitman, who died on August 13, 1999 at the age of 104, can be properly described as “the father of modern sleep research”. His claim on this title stems from both his scholarly integration of the work in the field and his own research. His 1939 compendium of prior work on sleep and wakefulness, revised in 1963 (18), includes thoughts on sleep ranging from Aristotle and other ancient thinkers to 20th century pioneers such as Pieron, Hess, Nauta and Kleitman’s contemporaries. The explosive recent growth of the field guarantees that this will be the last such comprehensive, research oriented integration of the literature in sleep research. In the introduction to the 1939 edition, Kleitman apologizes that his reading abilities are “limited to French, German, Italian and Russian” (and English). However, despite this “handicap” he critically integrates 4337 references covering sleep, circadian rhythms, sleep disorders, hibernation and theories of sleep function.

Kleitman’s research forms the foundation for many of the areas of current sleep research. His studies of sleep-wake and temperature rhythms in the isolation of Mammoth cave were a key event in the history of human circadian rhythm research. He carried out some of the first scientific studies of drug effects on sleep. His discovery with Eugene Aserinsky of REM sleep (4) is the key event in 20th century sleep research and led directly to the growth of the field in the last half of the 20th century. His work identified the developmental course of the human sleep cycle and highlighted the importance of ultradian rhythms. Indeed in what I believe was Dr. Kleitman’s last publication he emphasized the importance of ultradian rhythms, which he felt were more fundamental to sleep than the REM-nonREM cycle (19).

Dr. Kleitman pursued his research with inventiveness and determination. His “apparatus for determining and for recording motility and rectal temperature during sleep” (18, page 83) is a prime example, monitoring and timing bed movement and incorporating what can now be described as a primitive polygraph to produce a continuous readout of motor activity and achieve measurement that only recently became practical with microelectronic technology. His choice of the constant environmental conditions of Mammoth cave for his circadian rhythm studies necessitated his devising and incorporating traps to prevent rats from climbing into bed with the sleepers. This certainly would have been a confounding variable!

An exceptional rigor and conservatism in interpreting the results characterized all of his research. Eugene Aserinsky, Kleitman’s graduate student who died in 1998, relates the story of Kleitman’s skepticism about his discovery of REM sleep. After the initial finding made on Aserinsky’s son, Kleitman insisted that his own daughter serve as a subject. Aserinsky

surmises that this demand was to assure Kleitman that no fakery was involved in the presence of rapid eye movements while what appeared to be a waking EEG was present (3).

Dr. Kleitman was blessed with an exceptional intellect until the very end of his life. Well into his 80's and 90's I would often see him at the UCLA biomedical library, at research meetings in Los Angeles and at the annual APSS meeting, usually in the company of his daughter Esther. I was delighted to have the opportunity to organize a special symposium honoring Kleitman on his 100th birthday at the APSS (sleep) meeting in Nashville in 1995. It was with some trepidation that I asked him if he would be willing to talk about his career at the opening plenary session, attended by over 2,000 researchers and clinicians. I was comforted by the thought that Bill Dement who chaired the session would handle any problems that arose with kindness and tact. But Bill's sensitivity was not required. Kleitman gave a clear and moving presentation, explaining his fascination with the early work in sleep, the obstacles he faced, particularly the perception that sleep was not a proper subject for serious science and his amazement at the growth and impact of the field. Following the talk, attendees snapped up the specially reprinted edition of *Sleep and Wakefulness* and pursued him for autographs throughout the meeting.

This memorial volume incorporates reminiscences and biographic information by William Dement regarding his long and warm relationship with his mentor. Don Bliwise relates Kleitman's eagerness to help as a subject in his studies of sleep in the elderly and his feisty independence and resourcefulness. Monica Eiland and Oleg Lyamin of my group present the first studies of neuronal activity during reptilian sleep and use it to address the question of sleep evolution, an issue carefully considered by Kleitman in his book. Mircea Steriade relates his work with intracellular recording of neurons during sleep to the issue of active vs. passive theories of sleep that were a central aspect of Kleitman's work. Alexander Borbély considers issues of sleep homeostasis in the context of Kleitman's pioneering sleep deprivation studies. Dennis McGinty, Ronald Szymusiak and their collaborators consider the role of the hypothalamus and thermoregulatory mechanisms in sleep control, representing the modern development of the work of Hess, critically discussed by Kleitman. Kazuya Sakai presents a state of the art review of what we now know about the REM sleep state. In keeping with Kleitman's focus on motor activity during sleep, Ottavio Pompeiano presents his work on the role of locus coeruleus in muscle tone control across the sleep cycle. Leszek Kubin reviews work on cholinergic regulation of REM sleep. Larry Sanford et al. present work on the control of phasic events during REM sleep. Ronald Harper presents recent work on autonomic control during sleep and its relation to sudden infant death. Robert Moore et al. present the first description of the hypocretin neurons in humans, a system that has recently been implicated in REM sleep control and in narcolepsy. Emmanuel Mignot reviews the history of narcolepsy research, highlighting Kleitman as one of the early doubters of the psychosomatic theory of narcolepsy. Giulio Tononi and Chiara Cirelli discuss recent research investigating the role of REM and nonREM sleep in neural plasticity. Thomas Roth and John Roehrs discuss recent work on drug effects on sleep connecting these studies to Kleitman's pioneering investigations of the pharmacology of sleep. Scott Doran et al. discuss modern studies of sleep deprivation, building on Kleitman's pioneering studies in this area. Mark Mahowald and Carlos Schenck review the important clinical phenomenon of sleep state dissociation and its relation to the REM sleep behavior disorder and narcolepsy.

And finally Mary Carskadon et al. review the interaction of sleep loss and developmental changes, an area that is leading to changes in schedules for adolescents worldwide so as to maximize their night-time sleep and daytime alertness. The breadth of this work and commonality with Kleitman's work is testament to his scientific vision and the extent to which all sleep researchers are in his debt.

It is fitting that this tribute to Kleitman appears in *Archives Italiennes de Biologie*, the oldest Italian Journal of Biology, founded in 1882, and continued with Moruzzi and Pompeiano as a Journal of Neuroscience. It was in *Archives* that one of the first sleep deprivation studies in young dogs, performed by Manacéine, appeared (23), as well as the description by Tarchanoff (34) that both the arterial blood pressure and spinal reflexes were depressed during sleep. Much of the work by Moruzzi and his collaborators on the ascending reticular system and the sleep inducing structures as revealed in pretrigeminal or "encephale isole" preparations (5, 20, 27, 37) were published in *Archives*. In 1957, Rossi and Zanchetti (30) published a classic monograph on anatomy and physiology of the brainstem reticular formation. The *Archives* published key works by Sprague (33) and by the Scheibels (31, 32) on the reticular formation, by Magni and Willis (21) on the identification of reticular formation neurons by intracellular recording, and by Jankowska et al. (16) identifying brainstem mechanisms suppressing muscle tone. In 1960 Hubel (15) published a paper on the EEG activity in rats during natural sleep. The classic results obtained by Pompeiano on the descending inhibitory influences on the spinal cord during REM sleep (12, 13) as well as the work published by Pompeiano and/or his colleagues including Bizzi (6, 8), Morrison (24–26, 29), Hoshino (14, 28) and Mergner (22) on the cholinergic and vestibular control of REM sleep were published in *Archives*. Classic studies by Villablanca on sleep in the athalamic and diencephalic animals (35, 36) and by Bremer on control of the EEG (7) also appeared in *Archives*. The definitive lesion study in REM sleep control by Carli and Zanchetti (9) appeared in *Archives* as did Jouvet's classic review on REM sleep (17). Finally, it was in *Archives* that some of the key studies of the phylogeny of sleep by Allison and colleagues (1, 2) and by Rechtschaffen, Flanigan and others (10, 11) appeared. The current volume continues this tradition and represents the continuation of some of the many areas of research first explored and codified by Nathaniel Kleitman. Dr. Kleitman has left a great legacy to sleep research.

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**Fig. 1. -**  
Nathaniel Kleitman in undated photograph.





**Fig. 2. -**  
Kleitman monitors sleep of assistant Bruce Richardson in Mammoth cave.



**Fig. 3. -**  
Kleitman (center-right) and assistant Bruce Richardson (center) emerge from Mammoth cave on July 6, 1938.





**Fig. 4. -**  
Kleitman serves as subject in sleep study.



**Fig. 5. -**  
From left to right, Michel Jouviet, William Dement, Nathaniel Kleitman and Eugene Aserinsky, after their symposium on the discovery of REM sleep presented at the Nashville meeting of the Associated Professional Sleep Societies on June 1, 1995.  
The Symposium commemorated the 100th birth day of Nathaniel Kleitman in April 1995.