

REMEMBERING NATHANIEL KLEITMAN

W.C. DEMENT

Sleep Research Center, 701 Welch Road, Suite 2226, Palo Alto, CA 94304, USA

Nathaniel Kleitman was one of the professors teaching the neurophysiology course which I attended in 1952 during my second year at the University of Chicago School of Medicine. He had a somewhat brusque style of presentation, but his subject was fascinating. A few days after he finished his series of lectures I summoned the courage to knock on his office door and inquire if I could work for him. His response was to ask if I had read his book, *Sleep and Wakefulness* (10). When I admitted I had not, he suggested I do so. It was surely the most comprehensive monograph on sleep ever published (1st edition, 1939), but fortunately for me, extremely well written and easy to read. I returned a few weeks later to tell him I had now read it and was even more eager to work for him. We thus began a 47 year relationship which not only changed the course of my life but also greatly enriched it.

Nathaniel Kleitman was born in **Kishinev, Russia**, in 1895. He came to America in 1915 and received a BS degree **from what is now** the City University of New York in 1920 and an MA from Columbia University. After two years as an instructor in physiology and pharmacology at the University of Georgia, he returned to graduate school at the University of Chicago and earned a Ph.D. His doctoral research included observations on sleep deprivation. He was appointed to the faculty of the Department of Physiology in the Division of Biological Sciences at the University of Chicago in 1925 where he did research and teaching until he retired as a full professor in 1960. As far as I can tell his earliest scientific paper published in 1923 was "The effects of prolonged sleeplessness on man" (9). As is well known he carried out sleep studies in Mammoth Cave, Kentucky, and less well known, in underwater submarines during World War II, and studies above the Arctic Circle. He was keenly interested in 24-hour periodicities as well as shorter periodicities. The great bulk of his research contributions and concepts are included in *Sleep and Wakefulness* (10).

Although he made many research contributions during his professional career, Nathaniel Kleitman is probably most widely known for his discovery (with Eugene **Aserinsky**) of rapid eye **movements** during sleep (1, 2). I do not believe he ever **penned** a personal account of the motivations and thoughts that led to this **break-through** in sleep research. Self effacing to a fault, he snorted with scorn when I **once** asked if he **planned** to write his autobiography. For this special issue of *Archives Italiennes Biologie*, I thought it would be **appropriate** to **once again** **gather** up the threads of interest that **ultimately** led to Kleitman's decision to **observe** eye motility during sleep. What follows are my own impressions from **memories** of those early days.

Kleitman had become very interested in what he termed the “basic rest-activity cycle”. Being able to read Russian as well as other European languages, he was aware of the report of Denisova and Figurin (8) which described an impressively regular respiratory cycle in infants with a period of 50 minutes. He hypothesized that this short term periodicity ensured that a newborn infant would have frequent opportunities to respond to the stimulus of hunger pangs by waking up and crying, and would therefore get adequate nutrition. Other reports such as those of Ohlmeyer and Brilmayer (12, 13) suggested to him that the basic rest activity cycle was fundamental and tended to lengthen somewhat with age.

Kleitman was also very interested in “depth of sleep” and noted that all night depth of sleep curves were very different depending on the variable measured. He had read the report of Miles (11) and the Italian report by de Toni (14) describing slow rolling eye movements at the onset of sleep which appeared to decrease as sleep continued and presumably deepened. The neurophysiological conventional wisdom 50 years ago emphasized that large areas of the neocortex including the frontal eye fields were involved in executing oculomotor activity. All of this suggested to Kleitman that eye motility could be the most sensitive measure of the basic rest-activity cycle and also be more representative of changing brain activity, i.e. changing depth of sleep.

He then assigned graduate student, Eugene Aserinsky, to observe eye and body motility in infants. After Aserinsky had spent many hours watching the eyes of infants and had documented a reasonably clear basic rest-activity cycle in terms of non-specific eye and eyelid motility as well as body motility (3), Kleitman suggested including older subjects while he continued gathering data on infant sleep, a task for which I was now his assistant. Observations on infants could be conducted in the daytime, but observations on adults could not. In the first place, the daytime naps of adults were usually not long enough to document the basic rest-activity cycle. Some of our fellow students suggested using shift workers. However, the day sleep of shift workers could not be regarded *a priori* as normal, and moreover, shift work was much less prevalent in the late forties and fifties.

The only recourse was to observe at night. Staring at the closed eyes of infants was tedious enough, but staring at the closed eyes of human adults by the dim light of a 30 watt bulb in the middle of the night was sheer torture. Necessity being the mother of invention and torture being even more compelling, Aserinsky searched for a better way and came across the technique of electrooculography (EOG). Though the equipment used to amplify eye movement potentials was very primitive, it was infinitely more preferable to direct observations.

I wish I had a photograph of the old Offner machine with its thin paper role and its single pen. Fortunately, the American Heart Association had donated a four channel Grass **Model III** ink-writing oscillograph to the Department of Physiology and Aserinsky was permitted to use it at night. Up until this point, no distinction had been perceived in terms of rapid versus slow eye motility. Rather, each successive 5 minute epoch was designated “motility” or “no motility.” And so it was that amidst the giant haystack of sixty cycle artefact, electrode problems,

amplifier problems, and constant clogging of the pens, the needle of rapid eye movement EOG potentials was finally found (1, 2)!

I have often wondered where we would be today if Aserinsky and Kleitman had not discovered rapid eye movements during sleep. As should be obvious to one and all, even with this breakthrough, progress has not been at light speed. Given that sleep research and sleep medicine are still struggling to become full partners in the biomedical health research enterprise in the Year 2000, it seems likely that sleep medicine would not exist today if Kleitman had decided to do something else. The accomplishments of basic research would certainly be a **much smaller** component of our knowledge base; and biological rhythm research, which had independent origins, might still be talking only about rest activity cycles and erroneously equating rest and sleep.

Even after the reports of the occurrence of rapid eye movements during sleep were published in *Science* and in *The Journal of Applied Physiology*, there was an amazingly pervasive skepticism. In one of our regular meetings, a frustrated Kleitman suggested that I should take movies of the rapid eye movements so that incontrovertible proof was readily available. In 1954, video cameras had not been invented, technicolor was not available, and 8 mm movie cameras had not been developed. I was forced to rent a large and cumbersome 16 mm movie camera and to use black and white film. Kleitman volunteered to be the first sleep movie star. He insisted on coating his eyelids with black grease which he thought would better reflect the movement of the corneal bulge under the closed eyelids. He was a remarkable apparition with his two black eyes, but sadly I did not save the movies. The reason was that I did not capture any rapid eye movements on the film. Whenever I saw eye movements and started the camera, Kleitman would either awaken in response to the noise it made, or somehow the noise would cause the eye movements to stop. One night when Kleitman was unavailable, I asked a classmate to volunteer; for the record, his name was Faylon Brunemeyer. I got excellent movies of rapid eye movements the very first night. Kleitman and I assumed that because he was only 25, he slept much more deeply. Back then, I had no idea that medical students had huge sleep debts.

Dr. Kleitman was always willing to volunteer for all night sleep recordings. The first time I ever recorded him was for the purpose of obtaining all-night EEG and EOG data from an older person. He was then 59 years of age. A short while after he fell asleep, the EEG tracing showed what appeared to be a continuous spike and wave pattern which looked like petit mal or some other form of epileptic seizure activity. This pattern actually dominated the brain wave tracing for much of the night. There was obviously no overt movement or convulsion associated with the patterns, but it was extremely alarming to me. I considered other possibilities including brain tumor. In the morning, Kleitman hopped out of bed, rested, energetic, and apparently completely healthy. The primitive (by today's standards) vacuum tube amplifiers available in the 1950's made artifact and reality sometimes indistinguishable. I therefore decided to record Kleitman a second night before I said anything about his "abnormal" EEG patterns. To my heartfelt relief, his

brainwave tracings were completely normal all night long. Why so much electrical artifact occurred on the first night can only be explained by the vacuum tube gremlins.

On another occasion, I added respiration and EKG to the brain wave and eye movement recordings. Kleitman's breathing during sleep was about as normal as it could possibly be. In preparation for this paper I searched for the original paper and ink recording from that night which I am sure I have saved somewhere. I didn't find it, but there is a sample of his respiratory pattern in an early book chapter (4). I have also often wondered where we would be today if back then I had discovered that Kleitman was a victim of obstructive sleep apnea (see the Bliwise contribution in this journal).

During my 4 1/2 years (1957-62) at the Mount Sinai Hospital in New York City, my wife, children and I lived in half of a large apartment and the other half was a sleep laboratory. Kleitman would always stay with us when he was in town. The sleep laboratory was a convenient guest bedroom where I also recorded his all-night sleep patterns on many occasions. He was one of the first subjects upon whom I carried out selective REM sleep deprivation. At the age of 66, he showed the typical increase in "REM pressure" and recovery REM rebound.

My very first impression of Nathaniel Kleitman from attending his lectures was that he was down to earth and very well informed. He had an efficient, no-nonsense approach to things. As I got to know him better, I was awestruck by his erudition. He read, as he modestly confessed in the preface of *Sleep and Wakefulness*, only five languages, and apologized for not reading the Scandinavian languages and several others. So, with just a little help from his friends he was able to cover the total world literature dealing with sleep. He also spoke French, Russian, and I think German fluently. On several occasions when we were his guests for dinner and there were others present, his command of every issue discussed was truly amazing. He was conservative and economical in his personal life, but I was delighted as I gradually learned that he was a genuine populist, humanitarian, and liberal.

By the end of 1955, I had carried out only one all-night recording of a woman's sleep (5, pp. 39-40). With foresight into the future, Dr. Kleitman absolutely forbid additional sleep recordings on women unless there was a female chaperone present. I was seeing a young woman who agreed to fill this position. I later married her for even better reasons. When Dr. Kleitman learned that I had been married he announced that he and his wife would like to have us for dinner. Then he asked me if I played bridge. Though taken somewhat by surprise, I sensed it mattered to him. I was trying to decide how to say no and retain his respect when I heard my mouth say yes. I was aghast at what I had done because I had never played bridge. In one instant, I had become a fraud - an imposter. Fortunately, my wife was a very good player and, doing almost nothing else in the several days before the "dinner and bridge" engagement, she managed to teach me the rudiments of the game.

The day of reckoning came all too soon and with great trepidation we arrived at the Kleitmans' home. We were awestruck by the original Picasso in their entry hall and charmed by his gracious and welcoming wife. After a lovely dinner, the

cards were dealt. Lady Luck really took pity on me that night - my bridge hands were so good it was difficult to make a mistake. I was not exposed as the fraud I had felt, and one of the many things for which I am grateful to my friend, Dr. Kleitman, is that my wife and I have been playing bridge consistently and as often as possible ever since that first game 44 years ago. Many of those games were with the Kleitmans and after Mrs. Kleitman's death, with my mother or Mary Carskadon as the fourth when he came to visit us at Stanford.

If one plays bridge only for enjoyment and not for competition and prizes, it is one of the most pleasurable and sociable activities in the known world. During many afternoons and evenings at the bridge table, with lots of conversation and stories, I came to know and love Dr. Kleitman and to look forward with keen anticipation to visiting him or vice versa. He was simply a wonderful person, thoughtful and generous, with something interesting to say or a well justified opinion about every subject. We occasionally did other things, but he and Mrs. Kleitman loved bridge, as did my wife and I, and if possible that is what we did.

After graduating from medical school in 1955, I postponed my internship to continue the exciting studies of rapid eye movements and all night sleep patterns (6, 7). I also decided I might as well turn my own sleep research into a Ph.D. thesis. However, in addition to course work and research, this decision carried with it the formidable requirement of demonstrating proficiency in two additional languages. Whereas Kleitman was a remarkable multi-linguist, my talent for learning other languages has always been close to zero. To make things worse, there were two proficiency exams for each language. The first examination, administered by the Division of Biological Sciences, was paper and pencil and tested vocabulary and simple translation from English to the language in question and from the language to English. The second exam was administered to the Ph.D. candidate individually by a member of the faculty in the department in which the candidate was studying.

The day of my departure from the University of Chicago was quite memorable. I had chosen French and German as my two languages. Amazingly, I passed the two Division exams. However, I knew I was not verbally proficient. I procrastinated and procrastinated about taking the department exams. In addition, no one mentioned these lapses even after I had passed my thesis defense. I actually convinced myself that the department exams, which were somewhat informal, had been forgotten. I was to learn otherwise. My wife and I had packed our trailer and were about to drive out of Chicago to New York City for my internship. I went to Kleitman's laboratory for the last time to say goodbye. After a few amenities, he said, "By the way, you haven't had your French exam". He handed me a foreign research article to translate, thinking, I am sure, it was a mere formality and I would have no problem. Within a few minutes it was obvious I was not going to pass the exam. Neither of us quite knew what to do. Then he asked, "What about your German exam?" I admitted I had neglected that one also. Was I ever embarrassed!

He then told me to call the professor (for the record, Arno B. Luckhardt) who administered the German exam. So I made an appointment and my wife and I drove

to the residential area where he lived. Providence once again intervened on my behalf. It happened that I was a fan of Professor Luckhardt's favorite German poet. He sat and read poetry to me for some time while my wife waited outside in the summer heat; but as long as he wanted to read, I wanted to listen. He finally told me I was a "nice young fellow" and he passed me. So we left Chicago with the failed French exam and an unfinished thesis as the only obstacles between me and a Ph.D degree. Later on, Kleitman said if I would simply translate something in writing, he would accept it. This was very kind and he made it even more easy because he allowed me to use a dictionary. Although Kleitman was a stickler for the rules, he was also flexible and compassionate.

Nathaniel Kleitman is one of the prime examples of the folly no longer perpetuated in American Universities of forcing brilliant men to retire at 65. He lived on to 104 and was productive in many of those years in spite of first caring for his ailing mother and his beloved wife when she became ill. He never failed to keep up with the vastly expanding field of sleep research and all the related issues and controversies.

He moved to California shortly after his retirement in 1960 and I came to Stanford University in 1963. He always asked about what was going on in my personal life. He sent wedding presents, gifts when my grandchildren were born, and a never-ending supply of Christmas gifts of food or candy. When tragedy struck our lives he was more than sympathetic; he was grief stricken for us.

At the time of his retirement he requested me to finish his revision of *Sleep and Wakefulness* if he did not live to complete it. A novice in my career with young, non sleeping (of course) children, it was only my loyalty and love that persuaded me to make the promise I prayed, for many reasons, that I would never have to keep.

As is well known, Nathaniel Kleitman finished the 2nd edition of *Sleep and Wakefulness* in 1963, complete with 4337 citations and a very excellent index. It was certainly a staple for sleep researchers in those years but eventually became out of print. It was therefore a wonderful idea by our current editor, Dr. Jerome Siegel, then Program Chairman, to ask the University of Chicago Press to publish a special edition for the 1995 APSS meeting in Nashville, Tennessee. This was also the occasion of a great celebration of Kleitman's 100th birthday. Kleitman attended the meeting accompanied by his daughters Esther and Hortence, their husbands, and other relatives.

The meeting opened with a special symposium in which Professor Kleitman presented the leadoff paper on a panel that also included Michel Jouvet and the late Eugene Aserinsky. There was an enormous, eight foot high (not real but a very good imitation) birthday cake, and more than 2,000 members of the sleep community stood and sang, "Happy Birthday". Throughout the meeting, a crowd of people followed him around, asking him to autograph his book, taking photographs with him and repeating birthday wishes. It was as if he were a rock star. It was a magnificent, wonderful occasion that he totally appreciated. I visited him several times after that meeting and he always mentioned it.

Nathaniel Kleitman, my brilliant, staid, professional colleague was also a dedicated and loving friend. We miss him very much, but we were blessed to share his company for such a long time.

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