Sleep Advances, 2023, **4**, 1–5
https://doi.org/10.1093/sleepadvances/zpad002
Advance access publication 19 January 2023
Living Legends in Sleep Research

Living Legends in Sleep Research

Long day's journey into sleep

David J. Kupfer* and Ellen Frank

Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

*Corresponding author. David J. Kupfer, Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA. Email: kupferdj@upmc.edu.

Abstract

My long day's journey into sleep began as an adolescent trying to manage my evening chronotype. The relief, I felt when my undergraduate finals were scheduled at night and as a medical student being able to select psychiatry over surgery deepened my interest in sleep and chronobiology. That interest was allowed to flourish at the National Institute of Mental Health and then at Yale Medical School in setting up a sleep laboratory. The decision to move to the University of Pittsburgh in 1973 led to a 42-year adventure in which we were able to initiate research efforts on the psychobiology of depression. Our interest in social zeitgebers (daily routines) led directly to the development and testing of a treatment intervention for mood disorders, interpersonal, and social rhythm therapy. Our continued emphasis on sleep and circadian rhythms convinced us that sleep and circadian factors were central to all of health, based on the importance of connectivity between sleep and major metabolic and cell functions. This ongoing research motivated our strong desire to study the developmental aspects of sleep. Our success was influenced immensely by the presence of young scientists and a strong subsequent interest in career mentoring. Finally, as we left Pittsburgh in 2015, we became involved in the field of continuous objective monitoring using the commercial smartphone's behavioral sensing capabilities. Our journey is not over. We hope to explore the potential of these remarkable devices to improve our understanding of sleep/wake and circadian factors across all of health.

This paper is part of the Living Legends in Sleep Research series, which is sponsored by Idorsia Pharmaceuticals and Jazz Pharmaceuticals.

Keywords: sleep; circadian rhythms; depression; social zeitgebers; social rhythms; objective monitoring; digital biomarkers

First Steps Along This Journey

Rockville Centre, NY – 1955

For years, I would be fooling my parents into thinking I had gone to sleep by carefully turning off my bedroom light, waiting a few minutes, and then reading under my blanket for a good couple of hours with my flashlight. As I moved into adolescence, not surprisingly, I found my friends and I were all staying up late, but I was up later than any of them. It made me wonder what was different about me.

New Haven, CT – 1959

As my freshman year was coming to a close, the Yale campus was one massive construction site. This meant a limited number of rooms where exams could be held. The solution: move half of the exams to evening hours. While my classmates were complaining bitterly about this situation, I knew instinctively it would be a boon for me. Again, I wondered why I was thrilled with this arrangement when others thought it was a disaster.

New Haven, CT – 1964—deciding not to be a surgeon, a chronotype decision

That fortuitous exam schedule change and my resulting good grades were probably at least partially responsible for my being accepted to Yale Medical School. Although I did quite well in my surgery rotation and found the work fascinating, as I was learning more about myself and my chronotype (a word that was not yet part of my vocabulary), I knew surgery with its 06:00 am start times, was definitely not for me. The last specialty I ever thought I would consider was psychiatry, but a few charismatic professors who thought that mental disorders might actually be medical illnesses with a biological basis, captured my interest sufficiently to make me eligible to do a residency in psychiatry.

New Haven CT – 1966—looking for objective measures in psychiatry—sleep as a useful strategy

But, for me, psychiatry had one glaring deficit: the lack of objective measurement. No blood pressure cuff, no stethoscope, and no blood tests. This made me think about what changes occurred in mental disorders that we did have the capacity to measure. Sleep was an obvious one. With that in mind, I conceptualized and wrote my first peer-review paper on sleep [1], quickly followed by a paper on nurses' ratings of patients' sleep [2].

Bethesda, MD – 1967—able to do sleep research

Knowing that there were serious sleep laboratories at the National Institute of Mental Health's (NIMH) Intramural Program, and that

Submitted for publication: September 28, 2022; **Revised:** December 24, 2022

my options under the Berry Plan were Vietnam, Germany, or the Public Health Service, I applied for and got the opportunity to become a research fellow in the NIMH Intramural Program as my second- and third-year psychiatric residency experience while at the same time fulfilling my military service obligation. There I had the opportunity to do EEG sleep research as well as research on biological correlates of psychiatric disorders, particularly schizophrenia [3]. I left the NIMH the proud author of an article on sleep that was published in the *American Journal of Psychiatry*. This seemed like the first recognition that EEG sleep might be an important objective biomarker in a major psychiatric disorder.

New Haven, CT – 1969—set up a sleep lab

I returned to New Haven to finish my residency and was able, with engineering help, to set up my own somewhat primitive and cobbled-together sleep laboratory. There, I started studying the biology of mood disorders and was able to captivate a number of very talented medical students—some of my first real mentees—to help me with this work. Among them was Chip Reynolds who ultimately came to be a major figure in the field.

New Haven, CT – 1971—research career development award in sleep to study mood disorder biology; really interested in REM sleep

That work formed a strong enough empirical basis to enable me to get a Research Career Development Award to study sleep physiology and psychopharmacology in mood disorders and begin to address my very strong interest in REM sleep [4]. I thought the path forward at Yale was clear for me. But then Tom Detre decided to accept the position of chair of psychiatry at Pittsburgh and wanted me to follow him there. The opportunity was extremely tempting in many ways, but my four kids were settled in New Haven, things were going well for me academically and I had spent almost half my life as a Yalie. Could I trade the blue and white for the black and gold? I just did not know what to do.

Then, just about a week before I needed to make my decision, Franco Harris plucked a football out of the skies and turned it into a game-changing victory for the Steelers. The city of Pittsburgh went wild, and I took it as a sign from the heavens. This was where I was meant to be.

Pittsburgh, PA – 1973

Tom, bringing 27 of us from Yale to Pittsburgh, had negotiated for remarkable clinical and research resources. At this point, sleep research in humans was getting some attention from neurologists, but not much else. There was interest in REM/NREM sleep primarily in animals and little attention to the relationship of sleep to psychiatric problems. However, the real attention to sleep in psychiatry was focused on sleep and dreaming. When I arrived in Pittsburgh, the notion of human sleep research was accepted, but it was not considered central to health or disease. Within two decades that was to change dramatically. Today, one can hardly pick up a copy of the *New York Times*, the *Wall Street Journal*, or *USA Today* without seeing an article on some aspect of sleep or circadian rhythms.

In Pittsburgh, I was able to set up a real sleep laboratory with state-of-the-art equipment and a team of engineers, technicians, clinicians, and the most precious of all commodities in academia: space. We had a sort of motel of six fully outfitted sleeping rooms and a lounge where outpatients and normal volunteers having sleep studies could hang out until their studies began. In addition, we were able to wire 30 inpatient beds for sleep studies. With this comparatively luxurious setup, our research group was well positioned to pursue three parallel tracks, one focused on mood disorders treatment, biology, and sleep, one focused on sleep across the life cycle, and one focused on circadian rhythms. With the increasing understanding of disorders of sleep itself, our sleep lab quickly became a sleep clinic as well, one of the first in the country. Within a few years, our group received NIMH funding for Clinical Research Center (CRC) focused on mood disorders that enthusiastically embraced sleep as important to all psychiatric disorders and the need to monitor sleep as a barometer of mental health [5, 6]. The CRC also provided the venue for research training and career development that enabled junior colleagues including Dan Buysse, Michael Thase, Tica Hall, Ann Germain, and Tim Monk interested in sleep and circadian rhythms to initiate their careers. Not only did we look at the effects of various pharmacotherapies on the sleep of individuals with depression, but we also examined the effects of manual-driven short-term psychotherapies such as Beck's cognitive therapy and Klerman and Weissman's interpersonal psychotherapy on sleep over the course of depressive disorder.

Edinburgh, Scotland, and O'Hare airport 1975—the association of sleep disorders centers is born

By 1975 a handful of centers had begun to study patients during sleep. In addition to Stanford and our group at Pittsburgh, Montefiore Medical Center in New York, Ohio State University, Baylor College in Houston, and University of Cincinnati Medical Center were conducting overnight EEG sleep studies. At the Edinburgh sleep conference in 1975, Peter Hauri organized a lunch meeting during which a group of interested parties was formed. Later that year, we met at O'Hare airport and decided to form a sleep-center-oriented new organization that would focus on both medical and research aspects of human sleep. We called our new organization the Association of Sleep Disorders Centers led by those who are experts in both scientific investigations as well as clinical practice. This decision was instrumental in gaining the acceptance of sleep medicine within mainstream medical thinking.

The Macarthur Foundation Research Network on the Psychobiology of Depression: a Leap Forward on the Journey

To understand the impact of the MacArthur Network on our understanding of sleep and circadian science, one needs to understand the composition of the network and the Foundation's philosophy of how research could move forward. The Foundation believed that by bringing together experienced researchers and members of their laboratories who were focused on a problem from highly diverse points of view. Thus, the depression network included members ranging from the most basic molecular science to epidemiology and statistics.

One of the major areas of focus of the depression network was to try to understand circadian rhythms from both clinical and basic science points of view. Indeed, there was a circadian rhythm task force. The Network funded pilot research by both network members and promising young scientists. Among its proudest accomplishments was funding Joe Takahashi to develop mutant mouse strains, ultimately leading to his discovery of the *clock* gene.

With the support of Dennis Praeger, the program director, and Murray Gelman, a MacArthur Foundation Board member,

I was encouraged, on the basis of the Task Force's work to date to apply for funding the develop a circadian rhythm laboratory at Pittsburgh. That enabled us to create a light, sound, and motion-isolated "apartment" where we could pursue time-isolated studies of circadian biology.

Concurrent with this basic and translational work, a subset of the circadian task force including Cindy Ehlers, the second author (EF) and I began to pursue a long series of studies based on a hypothesis linking social and physiologic factors in the precipitation of mood episodes [7, 8]. At this point, what had been *my* journey became *our* journey in many respects.

We argued that daily routines or *social zeitgebers* played an important role in the entrainment of human circadian biology and, that in vulnerable individuals, disruptions in those routines could lead to a cascade of events ending in the complex of symptoms that constituted the diagnostic criteria for episodes of depression and mania. This led, in turn, to the development and validation of the Social Rhythm Metric, a self-report measure of "social rhythms," a methodology, based on the life events work of George Brown and Tyrell Harris, for assessing the rhythm-disrupting severity of life events and, ultimately, to the development and testing of a treatment intervention for mood disorders (interpersonal and social rhythm therapy) that focused on helping mood disorder patients to lead lives characterized by more regular social rhythms. [9–12]

Recurring Themes Begin to Emerge Along the Journey

As our own work in sleep and circadian rhythms moved along, so did the field both in the United States and internationally. The new tools of neuroscience, especially MRI and PET, enabled us to gain a richer understanding of how central these technologies were. In a similar fashion, genetics became an important tool leading, ultimately, to the discovery that we express circadian genes in virtually every cell in our body thus leading to the idea that **sleep and circadian factors are central to all of health**. With these discoveries came an interest in the **connectivity between sleep and major metabolic and cell functions** [13]. We also became interested in **developmental aspects of sleep**, as our work and that of others began to elucidate how sleep changes over the life cycle. Another major theme has been the **mentoring of young scientists** in the area of sleep research. Most recently, the availability of portable and wearable devices permitting the monitoring of sleep and other body rhythms has opened vast new possibilities for the **continuous, objective monitoring of health and management of disease in the natural environment.**

The centrality of sleep to all health

As we started studying various other parameters related to sleep, we could not help but recognize the correlation between sleep and endocrine function as well as with other circadian variables. This led us to pay more attention to the various metabolic systems including inflammatory processes and a variety of other 24-hour rhythms. Before we knew it, we were confronted with the fact that we were close to studying all of health, at least all of chronic disease, and the discovery by epidemiologists that individuals with major psychiatric disorders, particularly bipolar disorder, and schizophrenia, had much higher rates of chronic disease than age-matched individuals without psychiatric disorders. That, in turn, led us to study the interaction between so-called medical and psychiatric diseases and the role that sleep might play in that relationship. Several examples of these activities led members of our investigative group to study the relationship between cardiovascular disease and sleep and changes in various other cardiopulmonary parameters, including a strong interest in sleep apnea. This new emphasis also enabled us to begin to understand much more about the relationship of sleep to metabolic function in both obesity and diabetes. This led naturally to an interest in the effect of exercise on sleep and the effect of sleep on exercise capacity. All these activities confirmed our long-held hypothesis that sleep and its variations were central to all health.

Developmental aspects of sleep across the lifecycle

As our department's focus on childhood and adolescent depression and on depression in late life expanded, it became very clear that changes in sleep across the life cycle were vitally important in understanding developmental aspects of neurobiology and behavior in both those who are with and without psychiatric disorders. We paid considerable attention to childhood and adolescent sleep with a particular interest in normative developmental change during puberty and early adolescence. Many of these developmental changes were reflected in changes in 24-hour rhythms of which changes in sleep timing and sleep need were a critical part. The results of our studies of sleep in psychiatric disorders in adolescents and younger adults were remarkable for the extent to which the sleep of depressed young people was not that different from the sleep of healthy older individuals, especially with respect to fragmentation and the lack of slow wave sleep.

As mentioned above, our research programs in adult mood disorders were notable for the attention given to the relationship of sleep abnormalities and their amelioration with both pharmacotherapy and psychotherapy, but especially for our studies of changes over the course of treatment response, remission, and recurrence, with some patients having repeated EEG sleep studies over periods as long as 3 years.

In the area of aging, we established a considerable understanding of how normal sleep is affected in aging as well as how sleep differs in older individuals with and without mood disorders. The work in late life sleep developed its own center programs. The innovative work carried out in those programs revealed important relationships of sleep physiology to various disorders, psychiatric and physical, and among older individuals. The area of sleep and aging was particularly significant in that so many new biological systems come together and demonstrate their normal aging patterns or aging patterns that may relate clearly through psychopathology and early changes in neurobiology our own studies were able to demonstrate the put your aging phenomenon in sleep and how that related through specific issues in late life depression.

Mentoring young scientists

As the Pittsburgh sleep research efforts began to expand, we recognized that there was a clear paucity of well-trained clinical and basic investigators in the area of sleep and circadian rhythms. We turned to the availability of funding for postdoctoral training programs to begin to address that problem. Eventually, we were able to obtain funding to establish a series of eight postdoc training programs, many of which included a strong emphasis on sleep and circadian rhythm research. [14]

Unlike other institutions that found research career development awards too costly to support, we encouraged young faculty to apply for such awards and mentored them throughout the grant application process, from research problem conceptualization

through submission and, often, through resubmission. Once these young investigators were funded, we were able to ensure that they not only received the mentoring they needed but also were able to embed their work in ongoing programs that provided much-needed administrative and research assistant support that could not be charged to their award.

We also focused on the challenging transitions from career development awardees to first R01 funding and the transition from mentee to independent investigator. With respect to the first of these transitions, we encouraged career development awardees to be thinking about their first R01 application from literally their first day of funding and to recognize that, to avoid a gap in funding, they should plan for the fact that their R01 was unlikely to be funded on the first round. This focus seeded a whole generation, perhaps now two generations, of sleep researchers many of whom are now leaders in the field including Marc Ansseau, Dan Buysse, Pat Coble, Ann Germain, Tica Hall, Eric Nofzinger, Chip Reynolds, Debbie Sewitch, Isabella Soreca, and Michael Thase.

With respect to the transition from mentee to independent investigator and mentor of others, the intersection of sleep and psychopathology, and specific treatments for mood disorders opened new areas of research for young investigators and significant achievement in such areas including the relationship between imaging strategies and other neurobiological targets. These changes in research strategy allowed young independent investors to establish a partnership with other scientists in areas outside of psychiatry and stimulate more significant interaction across the entire medical range of medical specialties.[15]

Park City, UT – 2015—Continuous, objective monitoring of health, disease management in the natural environment, and digital intervention based on a social rhythm regulation model.

Long before leaving Pittsburgh, we had already developed an interest in actigraphy, home sleep recording, and apnea measurement methods; however, the development of the commercial smartphone opened horizons we could never have imagined even 10 years earlier. As we came to understand the enormous measurement capabilities of these intimate and nearly ubiquitous devices, we recognized that they were practically purpose-built for something we had never had in psychiatric medicine: continuous, objective measurement of disease-relevant behaviors. Indeed, we often say that what the smartphone can tell you and what you would want to know about a patient's behavior between visits was a kind of "marriage made in heaven" and that this was particularly true for individuals with bipolar disorder.

Initially, we partnered with colleagues from the Human–Computer Interaction Institute at our neighbor, Carnegie–Mellon University, in applying for Small Business Innovation Research funding to develop a smartphone-based Social Rhythm Metric; however, our NIH reviewers argued that there were not enough individuals with bipolar disorder to make this a viable business—only 3%–5% of the population if we include those with bipolar II disorder! Discouraged by this lack of awareness of the needs of these patients and the potential size of the market, we pulled a proverbial blanket over our heads (an apt metaphor for sleep researchers, no?) and turned to other pursuits.

Then, Mark Matthews, a brilliant digital technology postdoc from Dublin, arrived at Cornell University in Ithaca to develop technology for individuals with bipolar disorder. The only problem was there was no medical school in Ithaca and no easy access to individuals with bipolar disorder. He looked around the country for places where such research was being done and within weeks, Mark and our Depression and Manic-Depression Prevention Program at Pittsburgh had developed a plan to collaborate with individuals who suffered from bipolar disorder to create a research app that we called MoodRhythm, essentially a smartphone version of the SRM. We submitted MoodRhythm for consideration for a prize for the best new app at the 2014 Health Datapalooza Conference and won the $100 000 prize. Knowing absolutely nothing about business, we nonetheless decided that this was our opportunity to create one. We called it HealthRhythms. From its inception, the conceptual model for our products was based on the sleep/wake and social rhythm regulation ideas we had begun to evolve and study in 1988. Technology had caught up with our thinking and we felt ready to revolutionize measurement in mental health.

Fast forward 7 years and now we are able to demonstrate the capabilities of smartphone monitoring as digital biomarkers in pharmaceutical company studies, providing data that enable us to monitor and triage patients to the right level of care within health systems as well as sending just-in-time alerts to providers when patients are in need of immediate attention.

It took the development of the commercial smartphone to make monitoring patients' behavioral routines a practical, scalable reality, enabling us to understand the critical ways in which behavior affects physiology, and affects health. We can now leverage the passive sensing capabilities of the billions of smartphones around the world to identify behaviors directly related to a broad range of health parameters. Then, by (1) continuously and objectively measuring these parameters, (2) detecting changes in behavioral routines and health early, and (3) providing the opportunity for patients to learn, through digital or clinician intervention, how to lead lives characterized by more regular, health-supporting routines, we can improve clinical outcomes, avoid emergencies, and ultimately reduce the costs of care. [16]

When we moved to emeritus status at the University of Pittsburgh, we knew that we would be reinventing ourselves as we settled into life in Park City, UT. We just did not know that we would be reinventing ourselves as full-time entrepreneurs. Our work in founding and sustaining a rhythm-focused digital startup is simply the fulfillment of our lifelong dream to take a social rhythm regulation model and all of its potential benefits to the broadest possible swath of individuals both across the United States and throughout the world.

Conflict of Interest

The authors declare the following conflicts of interest: Dr DJK serves on the Board of Directors of Minerva Neuroscience, holds equity in Adaptive Testing Technologies, Inc. and is a co-founder of, consultant to, and holds equity in HealthRhythms, Inc. Dr EF holds equity in Adaptive Testing Technologies, Inc. and is a co-founder and Chief Scientific Officer of and holds equity in HealthRhythms, Inc.

References

1. Kupfer DJ, *et al*. Relationship between sleep disorders and symptomatology. *Arch Gen Psychiatry*. 1967;**17**:710–716. doi: 10.1001/archpsyc.1967.01730300070009.
2. Wyatt RJ, *et al*. A fourteen-symptom behavior and mood rating scale for longitudinal patient evaluation by nurses. *Psychol Rep*. 1968;**23**:1331–1334. doi: 10.2466/pr0.1968.23.3f.1331.

3. Kupfer DJ, *et al*. Sleep disturbance in acute schizophrenic patients. *Am J Psychiatry*. 1970;**126**:1213–1223.
4. Kupfer DJ, *et al*. Interval between onset of sleep and rapid-eye-movement sleep as an indicator of depression. *Lancet*. 1972;**2**:684–686.
5. Thase ME, *et al*. Electroencephalographic sleep in psychotic depression: a valid subtype. *Arch Gen Psychiatry*. 1986;**43**:886–893.
6. Kupfer DJ, *et al*. Electroencephalographic sleep profiles in recurrent depression: a longitudinal investigation. *Arch Gen Psychiatry*. 1988;**45**:678–681.
7. Ehlers CL, *et al*. Social zeitgebers and biological rhythms: unified approach to understanding the etiology of depression. *Arch Gen Psychiatry* 1988;**45**:948–952.
8. Monk TH, *et al*. The Social Rhythm Metric: an instrument to quantify the daily rhythms of life. *J Nerv Ment Dis* 1990;**178**:120–126.
9. Kupfer DJ. The mission of therapeutics presented at the 1992 ACNP Annual Meeting held in San Juan, Puerto Rico December 1992: "The First Gerald Klerman Memorial Lecture". *Neuropsychopharmacology*. 1993;**9**:169–180.
10. Frank E, *et al*. Interpersonal and social rhythm therapy for bipolar disorder: integrating interpersonal and behavioral approaches. *Beh Ther*. 1994;**17**:143–149.
11. Monk TH *et al*. Circadian rhythms in healthy aging--effects downstream from the pacemaker. *Chronobiol Int*. 2000;**17**:355–368.
12. Malkoff-Schwartz S, *et al*. Social rhythm disruption and stressful life events in the onset of bipolar and unipolar episodes. *Psychol Med*. 2000;**30**:1005–1016.
13. Leboyer M, *et al*. Can Bipolar Disorder be viewed as a multi-system inflammatory disease? *J Affect Disord*. 2012;**141**:1–10.
14. Kupfer DJ New opportunities and challenges for teaching and training. *Acad Psychiatry*. 2014;**38**:58–60.
15. Kupfer DJ, *et al*. Career development institute with enhanced mentoring: a revisit. *Acad Psychiatry*. 2014;**40**:424–428. doi: 10.1007/s40596-015-0362-5.
16. Frank E, *et al*. Personalized digital intervention for depression based on social rhythm principles adds significantly to outpatient treatment. *Front Digital Health*. 2022;**4**. doi: 10.3389/fdgth.2022.870522.