K24 CANDIDATES BACKGROUND AND GOALS FOR CAREER DEVELOPMENT

2.0 CANDIDATES BACKGROUND

It is difficult to precisely mark the beginning of my interest in the subject of sleep and dreaming, but the trajectory is clear from my undergraduate years at Guilford College to my present position as an associate professor at University of Pennsylvania. Each step of this path added immeasurably to my interest in, and experience with, our field. More than this, mentoring has been a core component across most of these education experiences, both by the generous example of my mentors and by my paying it forward to those that worked with me during each of these academic experiences.

2.0.1 Guilford College (1979-1983). My undergraduate education was in religious studies. This choice was in part because of my interests in mythology related to "beginnings and endings" and in part because the religious studies department had a core reading requirement that covered the majority of Freud's work, including the Interpretation of Dreams. This particular book (and the lectures related to it) served as my introduction to the possibility that dreaming, if not sleep itself, subserves a mental health related function. This experience, was coupled with two other cornerstone events that all but assured that my future interests would be related to sleep and dreaming. The first event was a requirement for an introductory abnormal psychology course to keep a dream diary for the first half of the semester and then to conduct a content analysis during the second half of the semester. The approach to the content analysis was to use Hall and Van De Castle's frequency analysis method (1966)[1]. I set an alarm clock for three awakenings per night and dictated whatever dream I recalled into a tape recorder beside the bed. By mid-semester, I had hundreds of dream logs which I transcribed and then subjected to frequency analysis. The number one "event" (as with many) was being chased. Unlike what is common, in these dreams I invariably dropped a shoe and, invariably, asked the pursuer to help me put the shoe back on, tie the shoe, etc. Unlike what is common, in these dreams the pursuer ceased to be hostile and was, in fact, helpful. Having been confronted with this recurrent theme, I recalled an actual event from my childhood, where this was precisely what happened one Halloween. This experience sold me on the idea that dreams are not random things. The second event was a personal experience, my first time being confronted with a sleep disorder. A friend of mine in college was sadly susceptible to frequent nightmares. What was particularly unusual was that she seemed to act out her dreams. When I queried my primary psychology professor about this, she informed me that this was not possible as dreaming occurred during REM sleep and that one feature of this state was paralysis. Interestingly, though I did not know it at the time (1983), Adrian Morrison had shown that REM sleep without atonia was possible (1981) and three years later Mahowald and Schenck described the first cases of REM Behavioral Disorder (1986). The combination of these events served as a foundation for my inchoate interests in sleep and dreaming; an interest that would be repeatedly reinforced over the course of my continued education.

2.0.2 West Virginia University (1984). In order to make myself eligible for graduate studies in psychology, I spent a year at WVU taking the required pre-requisite classes for my graduate school applications (e.g., statistics, research methods, psychology of aging, etc.). As part of my course on the psychology of aging we were required to write a term paper that was consistent with the focus of the course. For me this represented an opportunity to return to the subject of sleep and dreaming. I proposed to write a term paper on the dreams of the terminally ill. My take on the subject was that if dreams do indeed allow the individual process and/or resolve conflict or stress, then the dreams of the moribund (a word I learned during this endeavor) should be most instructive. After many trips to the library (scanning tomes that looked as ancient and as large as Moses's stone tablets), I came upon two sources of interest: a dissertation by Gary Groth-Marnat on "the phenomenon of dying as seen through the dreams of individuals with reduced life expectancy" (1977) and a one page article by Terry Beavers (1973)[2] on how dreaming could subserve a mood regulating function in a manner akin to behavioral systematic desensitization. What was proposed in this latter article seemed profoundly correct to me and from that point forward made my path clear: I wanted to conduct sleep research and specifically on this topic. While it would be nearly a decade before I published on this topic, the beginning of my academic path was set, though the path would not be a traditional one. For reasons that now elude me, I thought the best way forward was not to go directly to graduate school but to get a job working for someone whose life work was dedicated to sleep and dreaming. I did my best to identify sleep centers, the directors of these centers, and to write and query about possible employment. From the veritable salvo of letters, three individuals replied: Rosalind Cartwright PhD, Helmut Schmidt MD, and Wally Mendelson MD. Obviously, there was a clear match: Rosalind Cartwright. Dr. Cartwright, while a well-established sleep medicine specialist, had a well-known and well-articulated program of research on dreaming. As bad luck and good destiny would have it, the option with Rosalind Cartwright fell through and Wally Mendelson invited me to take up a technologist's position working for him in the Section on Sleep Studies of the Clinical Psychobiology Branch of NIMH.

2.0.3 NIH (1985-1987). Once again, as bad luck and good destiny would have it, the position Wally Mendelson had intended for me (working as a technologist in his human experimental and clinical research program) also fell through and he offered me a position working in his basic lab. Without a moment's hesitation, and

completely unprepared for, and unaware of, what basic research entailed, I accepted. The next two years were an immersion experience: an immersion into science (in general) and the science of sleep (in specific). Dr. Mendelson and his post-doctoral fellow Dr. Joseph Martin went to great lengths to make sure I was both technically competent (from animal neurosurgery & histology to rodent polysomnography [cable construction, instrument management and calibration, hookups, and sleep scoring]) and steeped in the neuroscience they were pursuing (an exploration of new hypnotics, their relative efficacy, and locus of action). It was my mission to pay back on their investment by learning all that I could and to show my appreciation by working long hours to accomplish the tasks set out for me, and more. I excelled in the position they had created for me and with time I became the go to person for our division to teach other technologists to conduct the animal surgeries, not only for the surgical implantation of EEG and EMGs, but also for the placement of micro-cannula for local site injections or electrolytic lesions. This was my first experience with mentoring and the concept of paying it forward. I was, in a word, enthralled with this form of one-on-one teaching and I suspected even then, that this would become a way of life. During the last year of my tenure with Dr. Mendelson, he extended my work profile to include collaboration on the analysis and write-ups of our data. While I had no idea of the value of this experience (or its currency value for academia), I enjoyed the process which resulted in at least a half dozen abstracts and my first 4 papers. Citations for three sample abstracts and the four papers produced during this period are listed in Appendix 1. The common thread in this work was the effort to 1) delineate which benzodiazepine receptor subtypes account for the hypnotic effects of endogenous (e.g., corticosteroids) and/or exogenous (i.e., barbiturates & benzodiazepines) receptor ligands, 2) determine the extent to which manipulations of cellular calcium and chloride flux mediate hypnotic effects, and 3) characterize the role of the anterior hypothalamus as a common site of action for a variety of sleep-inducing compounds.

In sum, my time at NIMH profoundly influenced my perspective on sleep research; it imbued in me the conviction that our field was inherently multi-disciplinary in nature and best informed by this approach. To the present day, I remain faithful to this point of view and not only embrace literatures beyond those that I specialize in (Behavioral Sleep Medicine) but I have actively sought out collaborations with investigators from the macro (epidemiology of sleep [e.g., work on national databases with Michael Grandner PhD) to the micro (basic science [e.g., a drosophila model of insomnia with Matthew Kayser MD, PhD).

In 1986 Wally Mendelson left NIMH to take up a position at the medical school at SUNY Stony Book. While I was invited to join him and to help build the new lab (an exciting prospect to say the least), I elected not to go. My feeling was that if I wanted to be a viable candidate for clinical psychology graduate studies, it was time to acquire skills and experience with patient oriented research. This opportunity came with a job offer from Steven James MD, who had worked in the chronobiology section of the clinical psychobiology branch at NIMH (space shared with the section on sleep Studies) and had recently moved from NIH to the University of Pennsylvania.

2.0.4 University of Pennsylvania (1987-1988). The job offered by Dr. James was to come to Penn and help him establish a sleep and chronobiology laboratory and to continue and expand the depression research he had conducted while a fellow with Dr. Thomas Wehr and Dr. Norman Rosenthal at NIMH. I accepted and moved to Philadelphia. Upon arrival it quickly became clear that it would be some 3-6 months before the laboratory was operational. I was given a clear mandate: 1) learn to conduct human polysomnography (hookups, data acquisition, and sleep scoring); 2) learn to use all the equipment in the laboratory; and 3) begin pulling, xeroxing, referencing, and filing articles related to sleep and depression. I pursued these tasks with ardor, evenly splitting long work days between these tasks. I was sufficiently adept at getting things done that Dr. James told me to set aside 1-2 hours a day to read the articles he was requesting and to meet with him weekly (frequently more often than this) to discuss the papers I'd read. Dr. James and I reviewed nearly the entirety of the existing literature on sleep and depression with him carefully and patiently explaining concepts and methods as we moved from study to study. This was my first contact with one on one mentoring and it demonstrated to me how valuable this style of mentoring could be. One other seminal event occurred while at Penn. On one of my many trips to the library, I came across Dr. Art Spielman's article "A behavioral perspective on insomnia treatment" (Psychiatric Clinics of North America, 1987)[3]. As with the Beavers' paper, what was proposed in this article seemed profoundly correct to me. Unlike the Beavers' paper, I did not see this as work that I would be pursuing; truly ironic given my eventual investment in behavioral sleep medicine and Cognitive Behavioral Therapy for Insomnia (CBT-I). This said, I purchased a hard copy of the journal and kept it in my library from then until now. My time at Penn (as learning intensive as it had been) ended with my acceptance into graduate school at University of Arizona.

2.0.5 University of Arizona (1988-1993). As is so often the case in history in general, and over the course of one's life in specific, it is hard to know that one is in the middle of something historic, game changing, and/or life changing. Being at UA was just such an event. The historic piece was that during the 1980s, psychology was suffering a balkanization with the whole of the field splintering into a host of would be independent disciplines including Neuroscience, Cognitive Neuroscience, Neuropsychology, Clinical Psychology, Social Psychology, Forensic Psychology, etc. Departments of Psychology nationwide were literally breaking apart

with different administrations, if not separate facilities. Under the leadership of the newly appointed chair of psychology, Lee Sechrest PhD, a different course was charted. The vision was that all the programs and laboratories would agree to a common core approach. The theme for the common core was human memory. Dr. Sechrest recruited new faculty that could add to the vision and promoted faculty who elected to contribute to the vision. By 1988 the department had been reconstituted and was populated by a group of luminaries (then or soon to be) including Daniel Schacter PhD, John Kihlstrom PhD, Lynn Nadel PhD, Ken Foster PhD, Mary Peterson PhD, Al Kaszniak PhD, and Richard Bootzin PhD. The summer I arrived was in many ways the commencement year of the new program and one of the kick off events was a national conference on sleep and cognition. This event was permanently archived in an APA publication which remains, even today, one of the best textbooks on this subject. An auspicious beginning. At my orientation meeting with Dr. Bootzin, he explained his approach to lab leadership, lab use, and his agenda.

Dr. Bootzin's agenda was that he wanted to outfit the lab to allow for split screen monitoring (video and EEG) and to find a way to conduct quantitative EEG analysis. He provided a budget for the implementation of these methods and set me on task. The former was easy to implement. The latter was in many ways a watershed project. First and foremost, I learned a valuable lesson: not all learning is explicit and deliberate. Sometimes learning is built on what one passively observes. In this case, I remembered that a regular ritual on Fridays at NIH was that a guest researcher (Richard Wagner MD) came to visit and spent the day with Dr. Martin running tape recorded data through the polygraph into a dedicated machine that produced an output with numbers assigned to categories. Even though I did not participate in this exercise, I vividly recalled the wiring for the apparatus and the procedural steps taken by the two investigators (a thing Dr. Mendelson had spent real time teaching me to do). On reflection, it occurred to me that the process I had observed was one where the EEG was being quantified. I pulled the paper "Frequency analysis of the sleep EEG in depression"[4] and gleaned from that paper what had been done and why. This was what Dr. Bootzin was looking for and after one failed attempt (using borrowed equipment) to precisely imitate the method, it occurred to me that the data storage process and the use of a dedicated calculator was probably unnecessary and some, or all of this, could be accomplished by computer. I went to the library and searched EEG Journals for advertisements for frequency analysis. Luckily, I found an ad for such a program and began communicating with the company. There were a host of problems in getting the software application useable for sleep research, not the least of which was how to manage the necessary sampling rates, number of channels, recording duration, file storage, screen resolution, and signal editing. In less than a year, and with a lot of help from the department's bio-engineering staff and the software company, the task was accomplished – Dr. Bootzin's lab was enabled to conduct QEEG. This methodology would later serve Dr. Bootzin's scientific aim (and my dissertation) on the association of alpha sleep with sensory and information processing during sleep in patients with fibromyalgia. Further, this technology would become a staple for my own research and for the majority of my career. The moral of the story (one I often share with trainees) is: while nothing replaces deliberate learning, one needs to keep one's eyes and ears open because what is passively learned contributes to the process.

Dr. Bootzin's policy regarding lab leadership and use was that the Sr. graduate student (which was me by default as I was his first student at UA) was to lead and coordinate lab activities and that the Sr. graduate student was free to use the lab for both informal and formal studies. Informal studies were those where we (the students in the lab) served as subjects and conducted pilot work on issues of interest (e.g., forced awakening protocols to assess perception of sleep and/or dream content, REM deprivation protocols and mood assessments, etc.). Formal studies were those that had protocols that were IRB approved and recruited subjects from the university or the Tucson community. One thing more in this regard: studies could only be run during the summer and only graduate students were allowed in the lab. At the end of the first summer, I met with Dr. Bootzin and asked if I could form a group to keep the lab running all year long, a group of dedicated undergraduates who would sign on for at least 1 year and for whom I would take sole responsibility for their training, sleep education, and the parlaying of their research experience into graduate school applications. Amazingly, Dr. Bootzin allowed this to go forward for a one year trial period. A 10 person group was formed and the experience was an unimpeachable success. Notably, two of the undergraduates from this research assistant cohort continued on in sleep research and have become leading figures in their respective areas (Sean Drummond PhD and Ken Wright PhD). Further, the success of this approach became a Bootzin tradition and continued until his passing in 2014. The work conducted within this model resulted in more than 25 conference abstracts and presentations and spanned a wide range of topics from GSR activity during sleep, skeletal muscle and facial EMG studies of waking and sleep, the McCollough effect (a visual aftereffect [5]) as a measure of sleepiness, a series of sleep and memory studies, and a series of studies on the alpha sleep as assessed with QEEG. Sadly, the one lesson I did not learn while a graduate student at UA was to translate pilot work and data into peer reviewed publications and/or grants. In fact, I did not realize that abstracts represented preliminary (if not incomplete) work until I interviewed for my clinical internship at Brown and was asked "why aren't there papers associated with all this work?". I didn't know what to say, but whatever I said seemed good enough as I was accepted into the program in 1993.

In sum, my training at University of Arizona culminated in 1) my master's thesis on skeletal muscle activity prior and during sleep and 2) my doctoral thesis on alpha sleep and on the association of alpha sleep with sensory and information processing during sleep in patients with fibromyalgia. The purpose of, and impetus for, my masters research was to follow up on Beavers' proposal that dreaming could subserve a mood regulating function in a manner akin to behavioral systematic desensitization. Since the theory was critically tied to the maintenance of a relaxed state during dreaming sleep (and since behavioral desensitization can be accomplished by muscle relaxation), I wanted to profile muscle relaxation during sleep and more importantly during REM sleep to assess if release from the motor inhibition of REM sleep occurred, for what duration of time, for which muscles, and whether this was associated with mood disturbance and/or psychopathology. The agenda for this line of research was delineated in my first 1st author publication, which was crafted over the first few years of my graduate training, but was not published until my clinical internship at Brown University[6]. The major findings for my master's thesis were: that skeletal muscle (postural muscle) activity is profoundly reduced (dysfacilitated) with the change in body position from standing to lying, that facial muscle activity is persistent until, and for some time after, sleep onset, that only the oro-facial muscles are persistently (tonically) active during NREM, and that the corrugator muscles are periodically phasically and tonically active throughout NREM sleep and occasionally active during REM sleep (and in a manner that occurs without parallel activity in the oro-facial muscles). Much thought and study was devoted to these findings (e.g., what is the consequence of the sudden and enduring loss of postural tone [not the least of which is a change in core body temperature], why are only the oro-facial muscles are persistently active [likely to enforce nasal/filtered respiration]; what is the meaning of periodic corrugator activity during sleep [e.g., appears to be a sensitive index of breakthrough activity because these muscle groups are the most resistant muscle to both endogenous and exogenous motor paralysis], whether micro-facial muscle activity as measured by facial EMGs predict dream affect or intensity [likely reflects intensity but not valence of experienced emotion], etc.). Unfortunately, only one of the resultant research projects was summarized as a peer reviewed paper, and this only much later during my post-doctoral fellowship at Western Psychiatric Institute and Clinics (sustained facial muscle activity during REM sleep and its correlation with depression[7]). The purpose of, and impetus for, my dissertation research was really directly attributable to both Dr. Bootzin and Dr. Mendelson. Both had an abiding interest in sensory and information processing and the formation of short and long term memory during sleep as core functional abnormalities in insomnia disorder. Dr. Bootzin believed that such abnormalities could be assessed with both cognitive neuroscience tasks and in terms of high frequency sleep EEG activity (alpha activity). The major findings for my dissertation were: Alpha activity was not associated with increased memory (implicit or explicit) for auditory stimuli presented during sleep, sleep state misperception, or with myalgia symptoms. Alpha sleep was found to be associated increased arousability (EEG activation in response to auditory stimuli) and the perception of shallow sleep. While unaware of it at the time, this work served a seed project for both my interests in the etiology and pathophysiology of insomnia and my (our) later articulation of the neurocognitive model of insomnia. Frankly, these ideas (and the resultant program of research) did not take root until I had a greater exposure to clinical work with insomnia patients during my internship at Brown University.

2.0.6 Brown University (1993-1994). The clinical psychology internship at Brown had three clinical rotations and a year-long research placement. The research placement was at the Sleep for Science Research Laboratory with Mary Carskadon PhD. Frankly, the allowance of even just a half day a week doing research (let alone with a luminary such as Mary) was what drew me to Brown. I was not disappointed. My half day a week was spent on a pilot research project validating a device that purported to provide core body temperature data from a sternal mounted sensor. My clinical rotations on the health psychology / behavioral medicine track included 4 months with Donn Posner PhD at the sleep and anxiety disorders program of Rhode Island Hospital, 4 months at the adult inpatient unit and partial hospital at Butler Hospital, and 4 months with Barbara Walker at the behavioral medicine clinic of Miriam Hospital. While all of the rotations were, in a word, educational, and all the rotations had clinical faculty the likes of which I had never seen (brilliant people absolutely dedicated to clinical work), my time at the sleep and anxiety disorders program with Donn Posner PhD was a game changer. It made manifest what had been absolutely latent until that time: my interest in CBT-I and insomnia research. Dr. Posner facilitated this intellectual metamorphosis in a variety of ways and observing him in clinic was a breath taking experience. His mastery of the method, his operationalization of the principles of the therapy, his delivery of the information to the patient, showed what it meant (and means) to be a master therapist. More than this, Dr. Posner enabled me (by example and with supervision) to do what he does, reliably produce robust clinical results. More than this, he sealed the deal by liberally sharing his time to directly encourage the intellectual engagement of the issues that exist at the interface between research and clinical practice. Over the course of many discussions, we framed more clinical research hypotheses and more education and practice goals than one career could ever encompass. More than this, Dr. Posner modeled the kind of mentor I would aspire to be, and am still working towards being. While I did not know it at the time, many of these things would come to pass, but would require yet another jump start by Dr. Posner at another time. I was not yet ready to shift, or rather bridge over, from sleep & depression research to insomnia research.

My hope, at the time, was that securing a post-doctoral position at Western Psychiatric Institute and Clinics would allow me to be able, finally, to focus on my pet hypothesis that mood dysregulation and major depression occurred, in part, due to a failure in REM sleep related desensitization of episodic memory.

2.0.7 Western Psychiatric Institute and Clinics (1994-1996). The two year research fellowship at WPIC was populated by a class of ~10 individuals each of whom were mentored by one or more program faculty. In my case my mentors were Daniel Buysse MD, Michael Thase MD and Donna Giles PhD. The fellowship had two major foci: learn to write papers and learn to write grants. To facilitate these goals, the program made data available from WPIC's vast archives and required that fellows attend a weekly writing seminar where both one's peers and WPIC faculty provided reviews of submitted work (in a manner deliberately similar to IRG review). During this time my training focus was primarily on becoming more facile with statistical programming and data summary in the form of manuscripts; the latter not having been a point of emphasis up and to that point in my training. While my interest in the desensitization hypothesis did not garner much interest and support, I was guided towards issues that were also of interest to me, more mainstream, and likely more publishable. The areas of investigation being related to 1) which sleep variable or variables (of all the sleep continuity and architecture variables) are most associated with depression severity (and which set of sleep variables load on cognitive/affective vs. neurovegetative symptomatology), and 2) if increasing insomnia severity is prodromal to new onset episodes of unipolar depression. These analyses were conducted in collaboration with a faculty statistician (Xin Tu PhD) and were written in collaboration with, and under the mentorship of, Donna Giles. Both of the papers stemming from these endeavors were nominated for the American Sleep Disorders Association's Young Investigator Awards. The working relationship with Donna is one I took to instantly, benefitted enormously from, and set the model for my own mentoring. Her approach was labor intensive and one that was phenomenally generous with her time: ideas were discussed and operationalized, the analytic plan was made plain, and the write-ups were conducted shoulder-to-shoulder, line-by-line. Eight papers were written during this time, including one pertaining to the desensitization hypothesis. Several intramural grants were also written during this period which, although not funded, served as a strong foundation for future such efforts. Finally, while at WPIC, at had my first experience with mentorship at a program level: I volunteered to assist the director of training for the Sleep Research Society (briefly with Mary Carskadon PhD, then Sonia Ancoli-Israel PhD, and then Dale Edgar PhD). This activity resulted in the institution of many of the training programs that exist today including: the publication of the first four editions of the training opportunities manual, the establishment of a trainee listserv, the inauguration of the annual trainee day at APSS, and the initiation of several SRS Jr. Investigator Grants. As, or more important, the experience reinforced my perspective that the pathways for training need to be made plain.

In 1996, Dr. Giles took an appointment at University of Rochester (UR), where she was provided a start-up package to build a sleep research lab and to start a sleep and depression research program, from scratch. Knowing that I had the technical skills to build a sleep lab, she asked if I would be interested in applying for a Jr. Faculty position with her in the Department of Psychiatry at UR. While I felt I was ready to begin working as an independent investigator (which of course I was not), I had the presence of mind to accept the overture.

2.0.8 University of Rochester (1996-2008). During the first years at UR I split my time evenly between overseeing the construction of the lab, acquiring clinical hours doing CBT-I, continuing to write up papers from WPIC, working on a series of grant applications, and the development of the neurocognitive model of insomnia. The lab opened its doors in 1997 and by this time I had successfully competed for four small grants (an R03, a NARSAD young investigator award, an ASDA (AASM) pilot grant award, and an UR intramural award) and published the neurocognitive model of insomnia (notably in collaboration with both Dick Bootzin and Wally Mendelson). The focus of the model was to reframe the problem of insomnia in terms other than presenting complaint and/or the face valid necessary relationship between hyperarousal and sleeplessness. The focus was to re-frame the etiology and pathophysiology of insomnia in terms of heightened exteriorception (i.e., a failure to inhibit or down regulate sensory and information processing) and/or the formation of short and/or long term memory for perceived events during the sleep period. Without realizing it at the time, I had begun to frame insomnia as a status disassociatus disorder (part sleep and part wake), a concept articulated by Mahowald and Schenck (broadly applied to a variety of sleep disorders, but not insomnia) and later explicitly applied by Daniel Buysse MD in the neurobiological model of insomnia. This line of research led to my first R01 and has been my primary focus since, along with the evaluation of factors that moderate the occurrence and severity of, or are consequences of, nocturnal wakefulness.

Given the tact toward insomnia research, we subsequently fielded several grants pertaining to CBT-I. My goal with these grants was to test 1) the limits of the treatment approach (i.e., that CBT-I outcomes will be attenuated in conditions where the percipient remains a "perpetuant", e.g., chronic pain), and 2) the potential of the intervention to produce good clinical outcomes in areas other than insomnia (e.g., reduce perceived pain intensity or increase pain tolerance). These efforts necessitated the creation of a research grade treatment manual. The manual was drafted over a series of weekend work efforts with Carla Jungquist NP PhD, Michael

Smith PhD, and Donn Posner PhD. Not only was the manner of creation unusual (a group shoulder-to-shoulder approach where every line was crafted collaboratively), but the manual itself was the first of its type to layout CBT-I in a standardized manner, session by session, with example patient-therapist dialogues crafted to model the management of the patient resistances that are part-and-parcel of CBT-I. While pursing the R21 projects that gave rise to the manual (R21NR009080 & R21MH067184), the finished product was published by Springer-Verlag (hardback in 2005 and paperback in 2008). Given my ardor for, and commitment to, teaching and the desire to disseminate this highly effective therapy, a companion continuing education workshop was initiated in 2005. Initially, the 3 day course was conducted by me, but in 2008 Donn Posner joined the workshop as a commentator and has continued on since. Dual teaching the course has transformed the endeavor into a highly engaging blend of clinical and research wisdom. Dr. Jason Ellis PhD joined in on our efforts in 2013. Since this time, the published manual has sold 7,264 copies, been downloaded more than 2500 times, and has been translated into 5 languages. The workshop has been offered once annually in the United States and has been offered by invitation in five different states in the U.S. and in 8 countries. The basic course generated such substantial interest that a second advanced course was created and has been offered since 2014. Overall, the workshops have had more than 1500 attendees (sample itineraries are presented in Appendix 2).

Finally, during the UR years, I continued my work with the SRS in support of its training program, established the Behavioral Sleep Medicine Group Listserv (1996 to the present, n=500+), and continued the tradition begun at the UA: the identification of outstanding undergraduates and their recruitment to assist with the day to day operation of the lab, trading my efforts to provide good training and academic opportunities for their hard work. This model continued to be successful and produced at least two individuals that are rising stars within our field: Sara Nowakowski and Michael Grandner. These individuals went on to graduate training at UCSD and presently hold academic posts at University of Texas (Galveston) and University of Arizona (Tucson). Both, to this date, remain colleagues and collaborators. In addition to these successes, I mentored or co-mentored four individuals as post-docs and/or Jr. faculty who are now well-established independent investigators including Mark Aloia PhD (National Jewish Health, Denver CO), Michael Smith PhD (Johns Hopkins University, Baltimore MD), Wilfred Pigeon PhD (UR) and Joseph Roscoe PhD (UR).

2.0.9 University of Pennsylvania (2008 to Present). In 2008, I had the exceptionally good fortune to be recruited to University of Pennsylvania. At the time, I had fielded several grants which were scored fundable and it made sense that if a change was to be made, this was the time to make that change. The grants spanned several subject areas within insomnia research and each were written in collaboration with colleagues who had dedicated and complimentary areas of expertise. The grants were focused on the following topics: Information processing in insomnia as assessed with ERPs (R21MH076855 w/ Kimberly Cote PhD); attention bias as an etiologic factor in primary and secondary insomnia (R01MH077900 w/ Colin Espie PhD); the relative efficacy of CBT-I as compared to zolpidem and trazodone (R01MH079109 w/ Dieter Riemann PhD); CBT-I +/- modafinil for insomnia and fatigue following chemotherapy (R01CA126968 w/ Joseph Roscoe PhD); and the role of partial reinforcement in the long term management of insomnia (R01AT003332 w/ Robert Ader PhD). One of these grants, while scored within a fundable range, was not awarded by program (the comparative efficacy study), two were left at university of Rochester (ERP and CBT-I in cancer survivors grants [note: a subcontract between Penn and UR was formed for the CBT-I in cancer survivors grant), and two grants were transferred to Penn as the basis for the establishment of a behavioral sleep medicine program in psychiatry (the attention bias and partial reinforcement grants). The Penn Behavioral Sleep Medicine (BSM) program was established in collaboration with the chair of psychiatry (Dwight Evans MD) and supported by Michael Thase MD, David Dinges PhD, and Allan Pack MD. I was recruited to direct the program and to establish it as part of the vanguard for our nascent discipline. Over the last 8 years, we have worked assiduously towards this goal. While much remains to be done, our program has a vigorous research base, offers a broad range of educational activities, and has a state of the art clinical service.

At the research level, we completed the three projects carried forward (or subcontracted) from UR to Penn. To date we have published our results from the partial reinforcement[8] and CBT-I +/- modafinil in cancer survivors[9] studies. We have also initiated several related programs of research including the

1) conduct of two natural history of insomnia studies (Co:PI[s]: MLP & Jason Ellis PhD)[10,11,12]

2) evaluation of nocturnal wakefulness (and/or sleep duration) as a risk for suicidal behavior (PI:MLP including one empirical paper [data in press with JCP], one conceptual article[13], and two collaborative publications, one with Rebecca Bernert PhD[14], and one with Suhbajit Chakravorty MD and Michael Grandner PhD[15])

3) assessment of the rhythm of insomnia: the non-randomness of symptom presentation over time (PI:MLP. Co-PI: Jackie Kloss PhD[16,17])

4) development of a brief but comprehensive screener for sleep disorders (Co-PI[s]: Karen Klingman PhD & Carla Jungquist PhD[18]).

5) conceptualization of the potential effects of sleep continuity disturbance on reproductive capacity and (Co-PI[s]: MLP & Jackie Kloss PhD[19]).

6) differentiation of insomnia and short sleep's (habitual sleep duration) association with self-reported and objectively determined diabetes and cardiometabolic disease (PI: Michael Grandner PhD[20-24]).

7) conduct of a CBT-I +/- modafinil study in patients with sleep disordered breathing (PI: MLP with Sheila Garland PhD. Data will be presented at the 2016 annual sleep meeting).

8) meta-analytic assessment of the subjective and objective effects of medications used to treat insomnia (PI: MLP with Waliuddin Khader BA, Elizabeth Culnan MS, and Jackie Kloss PhD). This work is in the data analysis phase.

At the educational level, we have a variety of free-standing education activities including: research assistantships for undergraduates and post baccalaureates; annual intramural BSM lectures within the medical school; our annual 3 day basic and advanced CBT-I seminars; a fellowship (via Dr. Pack's T32); a mini-fellowship program; clinical practice individual and group peer consultation services, and a training clinic for masters levels trainees to conduct CBT-I under the supervision of established experts.

At the clinical level, we have worked closely with the University of Pennsylvania Sleep Center and the Department of Psychiatry to establish a BSM service that provides not only the highest standard of care for insomnia (both with cognitive behavioral treatment of insomnia, CBT-I, and/or Pharmacotherapy) but also the provision of non-pharmacologic interventions for most of the intrinsic sleep disorders. We are presently piloting the ISR (Intensive Sleep Retraining) protocol to determine if this can be added to our available clinical services. The provider base is currently comprised of one psychologist (Dr. James Findley PhD ABSM CBSM) and three nurse practitioners.

In addition to these endeavors, our group fielded several professional related publications pertaining to the dissemination and implementation of CBT-I. The publications related to these efforts include one commentary (re: How can we make CBT-I and other BSM services widely available?[25]) and one data based paper (Where are the behavioral sleep medicine providers and where are they needed? A geographic assessment[26]).

GOALS FOR CAREER DEVELOPMENT

General

To expand the candidate's program of research to take into account how aging, or factors associated with aging, moderate the effects that have been his primary focus over the course of his career. Eight specific areas are listed below (in addition to the primary goals of the NHI study). It is anticipated the substantial progress will be made on each of these areas over the course of the five year award period.

1) cortical activations' association with the incidence, or severity, of insomnia
2) insomnia as a risk factor for, and a prodromal symptom of, recurrent and/or new onset depression
3) nocturnal wakefulness as a risk factor for suicidal ideation and behavior
4) the non-randomness of the incidence of insomnia
5) sleep homeostasis dysregulation and sleep discontinuity
6) placebo effects in patients with insomnia
7) The feasibility of partial reinforcement (Behavioral Pharmacotherapeutics) for maintenance therapy
8) the efficacy and limits of CBT-I

Specific

Each interest area is briefly explicated below with an emphasis on whether the issue can be addressed with data from our archives or on-going studies. In each case where data are available, we will identify a graduate

student, a post-doctoral fellow, or a junior faculty member from within our program to spearhead the proposed archival studies. Where possible, age interactions will be evaluated.

1. Cortical activation's association with the incidence, severity, or perception of insomnia. Our focus to date has been on the extent to which increased cortical activation (as measured with quantitative EEG [QEEG]) is a reliable feature of insomnia. While there is some evidence that beta EEG during NREM sleep increases with age[27], this issue has not been addressed by our group. We are, however, in the fortunate position of having two data sets on which such analyses could be conducted: 1) data from a collaborative R01 (R01MH077900) conducted with Colin Espie PhD (Glasgow/Oxford University) and 2) PSG data from the NIA funded parent grant for this proposal (R01AG041783 [NITES]).

2. Insomnia as a risk factor for, and a prodromal symptom of, recurrent and/or new onset depression. While there are a variety of studies that have shown that insomnia is a significant risk factor for new onset and/or recurrent depression[28] (one of which was conducted by our group in older adults[29]), to our knowledge only one study has evaluated insomnia as a prodromal sign of the disorder (i.e., state-wise exacerbation of insomnia heralds that an episode is imminent)[30]. One reason this work has not been replicated is that it requires very high temporal sampling rates over extended time intervals (daily to weekly assessments of sleep continuity over months to years). Once again the NITES data set could be used for such analyses given that up to 75 new onset episodes of depression are expected to occur, assuming a 5% incident rate per annum, across the three study cohorts.

3. Nocturnal wakefulness as a risk factor for suicidality (suicidal ideation and/or behavior). To date more than 40 studies have shown that sleep disturbance in general, and insomnia and nightmares in specific, are significant risk factors for suicidality[31]. This line of investigation can be followed up two ways. First, since the PHQ-9 is given during the NITES study on a bi-weekly basis, it will be possible to profile, in a within subject controlled fashion, the covariation between suicidal ideation and the preceding week's sleep profile and time awake during the night. Second, we have a grant application pending with NIMH, proposing to model nocturnal wakefulness using two forms of partial sleep deprivation in patients with depression where we will sample suicidal ideation, executive function, and QEEG assessed frontal EEG activity. In both cases, age will be assessed to determine if older adults are differentially affected. See Appendix 3a for an abstract.

4. The non-randomness of the incidence of insomnia. In recent years, the issue of night-to-night variability in insomnia severity has received increasing attention[16,17,32-34]. There are three schools of thought regarding when insomnia occurs over time: 1) its random[32]; 2) sometimes it's random, sometimes not[33,34]; 3) it's not random (occurs in predictable cycles)[16,17]. Our hypothesis that the incidence of insomnia is non-random derives from the perspective that since sleep is homeostatically regulated, and since sleep deficits can accrue across nights, the individual can only go a certain number of nights before the deficit is substantial enough to produce good sleep continuity. Our ability to resolve the non-randomness of insomnia (as a main effect) likely derives from 1) our access to night-to-night data for extended time periods, 2) the methodological approach of anchoring the time series data to a common event, and 3) by asking the question in this manner: "following an average or good night's sleep, how many days of poor sleep occur prior to the next instance of average or good sleep?". When operationalized in this manner, we have twice shown there is a rhythm to the incidence of insomnia. That is, the average bout length of insomnia (number of consecutive nights with poor sleep) is between 3 and 4 nights. Since the NITES study is gathering night-to-night data over the course of one year intervals, this issue will be revisited taking into account not only subject status (Good Sleep, Acute Insomnia, Recovery, or Chronic Insomnia) but whether age moderates the cycle length.

5. Sleep homeostasis dysregulation and sleep discontinuity. There is a long standing tradition that chronic insomnia (sleep discontinuity) is related to sleep homeostasis dysregulation. This derives from both theory[35,36] and empirical work[37]. The theoretical position espoused by the Behavioral Model of Insomnia, is rooted in the perspective that chronic insomnia is perpetuated by (irrespective of what may precipitate it) a mismatch between sleep ability and sleep opportunity. The mismatch (putatively caused by sleep extension [increasingly sleep opportunity to recover lost sleep which putatively results in diminished sleep pressure]) necessarily results in low sleep efficiency and what sleep does occur is likely shallow (less slow wave activity). Whether the development of chronic insomnia entails an inherent or developed deficiency in sleep homeostasis has not been established[37]. While a few sleep deprivation studies have been conducted to assess slow wave activity varies from baseline to recovery sleep, the results are inconclusive[37]. Another approach to this issue is to assess sleep homeostasis over circadian time (i.e., the interaction of Process C and S) using paradigms like a 90 minute day and/or a forced desynchrony paradigm in either the types (e.g., Psychophysiologic Insomnia, Paradoxical Insomnia, etc.) and/or subtypes (Initial, Middle, Late insomnia) of insomnia as compared to good sleepers, or in acute and chronic insomnia as compared to good sleepers. Such an evaluation will have to wait for the deployment of a dedicated experiment.

6. Placebo effects in patients with Insomnia. While many avenues of research within this arena are possible, our interest has been devoted to the possibility that placebo effects (when only placebos are utilized) derive from three factors: expectancy; naturally occurring contingent or partial reinforcement of expectancy (i.e., the co-incidence of pill use with good sleep); and the eventual conditioning of pill use to the physiology of good sleep (i.e., when pill use serves as a conditioned stimulus for the incidence of the physiology of good sleep)[38]. Please note that this perspective is not unique to insomnia but could be applied to any disorder whose severity naturally varies over time (though we suspect that the periodicity with which symptom improvement occurs probably needs to be 1 or more times per week). Insomnia represents an ideal case for placebo effects to be reinforced over time in that better than average or good sleep occurs, by definition, on up to 4 nights per week. These ideas could be further pursued (validated) by 1) obtaining and analyzing placebo data from long term randomized clinical trials (possibly from Industry Phase III or Phase IV trials), and/or 2) conducting dedicated studies where expectancy and conditionability are assessed a priori and evaluated for their association with the magnitude and durability of placebo effects. These ideas will likely be deferred in favor of assessing how placebos may act as conditioned stimuli for pharmacological effects (see below [subsection 7]).

7. The feasibility of partial reinforcement (Behavioral Pharmacotherapeutics) for maintenance therapy. While there are many reasons to be drawn to this line of research, three reasons in particular stand out. ***First,*** and perhaps foremost, is that the work is a natural extension of our research on night-to-night variability insomnia and our position that placebos may become conditioned stimuli for good sleep (i.e., with enough pairings, a placebo may come to elicit the physiology of good sleep) [38]. This notion is related to Dr. Robert Ader's position[39,40] that placebos can become condition stimuli for pharmacologic effects. ***Second***, in many ways this is a legacy project that seeks to complete work unfinished by Dr. Ader, i.e., to provide the requisite demonstrations that show that placebos can, and should, be exploited for their therapeutic value (as opposed to only be utilized as control conditions within experimental paradigms). ***Third*** (and related to the 2nd), is to provide the requisite demonstrations that show that the interposition of placebos along with active medication is an ideal way to: extend the efficacy half-life of medical maintenance therapies; reduce the incidence, or severity, of medication related side effects; reduce medication costs; and manage therapies with narrow therapeutic indices. To date we have conducted one behavioral pharmacotherapeutics RCT with zolpidem in patients with chronic insomnia[8]. It was found, in compliant subjects, that nightly dosing with 10mg, partial reinforcement at 50%, intermittent dosing, and nightly dosing with 5mg produced equivalent outcomes with respect to maintenance of treatment response overtime (i.e., prevent or delay relapse). For the subjects that remained in remission, the subjects in the intermittent dosing group exhibited poorer sleep continuity and tended to exhibit more medical symptoms than the subjects in the alternate groups. Presently, we have two grants pending on this topic: one on low frequency partial reinforcement with zolpidem in patients with chronic insomnia (see Appendix 3b for an abstract); and one on partial reinforcement with opioids in patients with chronic pain (Co-PI Carla Jungquist NP, PhD see Appendix 3c for an abstract). Both proposals will take into account age to determine if the observed effects are more evident in older adults.

8. The efficacy and limits of CBT-I. Over the course of the last decade we have had an abiding interest in 1) the *limits of CBT-I*, 2) *how CBT-I might be modified* to produce less attrition, greater compliance, and/or larger effects, and 3) *whether briefer versions of CBT-I have the same efficacy and durability* as standard 6-8 session treatment.

With respect to the first (the limits of CBT-I), Dr. Carla Jungquist and I undertook a controlled study of CBT-I in patients with chronic pain. This clinical population was selected based on the concept that pain serves as both a precipitant and a "perpetuant" of insomnia. Given that not only behavioral factors are in play, it was hypothesized that CBT-I would be less effective in this clinical population (compared to meta-analytic norms). To our surprise this was not the case. The results from our study were that 1) CBT-I was effective and the outcomes equaled or exceeded the meta-analytic norms, and 2) some evidence was garnered that the intervention produced improved pain tolerance[41,42]. Future work within this arena may include post hoc analyses to determine if the observed outcomes vary with age.

With respect to the second (how CBT-I might be modified), we have conducted four studies of CBT-I +/- modafinil; two of which were studies in subjects with uncomplicated Insomnia Disorder and two of which were in insomnia populations with excessive daytime fatigue and/or sleepiness (insomnia in cancer survivors and insomnia in patients with obstructive sleep apnea who are beginning PAP therapy). The rationale for adding a short term trial of modafinil to CBT-I was based on the following: 1) if one of the mechanisms of action of CBT-I is foreshortening the sleep (and extending the wake) period, then it follows that pharmacologically induced (and prolonged) wakefulness should have similar effects on sleep continuity (and potentially be additive to the effects of CBT-I); 2) if one of the rater limiters to compliance with CBT-I is transient increases in daytime fatigue and/or sleepiness, this adverse outcome (or iatrogenic effect) could be blocked with modafinil; and 3)

unlike combined treatment with hypnotics, patients would not be likely to attribute improved sleep continuity to the medication (which may undermine long term compliance with the tenets of CBT-I and therefore compromise the durability of outcomes typically seen with CBT-I). Only one of the two studies in patients with uncomplicated Insomnia Disorder has been published[43]. In that study, it was found that modafinil (100mg QAM) did not positively or negatively affect average outcomes with respect to sleep continuity. Daytime sleepiness and compliance with CBT-I (adherence to prescribed time in bed) were significantly improved. The second study was a pilot investigation of modafinil (100mg BID). These preliminary data, which suggested that modafinil alone (and in combination with CBT-I) improved sleep continuity, were used in an unsuccessful bid to secure NIH funding for this line or research. To date, two studies have been published from the project in cancer survivors[9,44] and no studies have yet been published from study in patients with insomnia and obstructive sleep apnea. In the studies of cancer survivors, CBT-I was found to produce significant effects with respect to both fatigue and sleep continuity. Armodafinil, alone or in combination with CBT-I, did not produce any therapeutic benefits (not for sleep continuity and/or fatigue or sleepiness). Future work within this arena will include post hoc analyses to evaluate if the observed outcomes vary with age and whether alternative measures (prospective sampling with sleep diaries) uncovers either sleep continuity or compliance effects.

With respect to the third (whether briefer versions of CBT-I have the same efficacy and durability as standard CBT-I), this issue has become more critical in recent years. The increasing awareness of the efficacy of CBT-I as a (or the) primary indication for chronic Insomnia [45] combined with the lack of providership[25,26] has spawned a movement to make CBT-I more available by making the intervention briefer (i.e., 2-4 sessions vs. the traditional 6-8 sessions). While the results of BBT-I have generally been good, and relatively comparable to the meta-analytic norms[(e.g., 46,47)] no studies have been conducted on the relative efficacy of BBT-I as compared to CBT-I. Such studies are needed to directly assess whether the two treatment modalities produce comparable outcomes (and for whom) and are similarly durable. To date, we have fielded one such grant proposal but were unsuccessful in the bid to secure funding (See Appendix 3d for the abstract corresponding to this grant submission). I suspect that this line of research will be pursued in the near future pending the interest of the NIH (particularly NIMH or NIA) and our junior faculty either at Penn or at the institutions with whom we regularly collaborate. Future work will take into account age as a potential moderator of outcomes.