Globalization has affected the medical research community much as it has economics, culture, politics and communications.
# Table of Contents

- Message from the Director: 2-3
- International Programs: 4-7
- Educational Initiatives: 8-11
- Fellowship Training Program: 12-13
- Basic Science Research: 14-15
- Patient Oriented Research: 16-17
- Clinical Program: 18-19
- Sleep Program at the Children’s Hospital of Philadelphia: 20-23
- Sleep Program in the Department of Psychiatry: 24-27
- Sleep Program in the School of Nursing: 28-29
- Faculty: 30-39
- Publications: 40-43
- Grant Support: 44-46
from
the
director

Drs. Allan Pack and Michael Perlis
This has been a wonderful year for Penn Sleep despite the challenging economy. Our faculty are receiving important recognition. Our research portfolio remains strong. Our junior faculty successfully competed for new resources provided by the American Recovery and Reinvestment Act (ARRA). Our graduate students’ accomplishments have been recognized, and we continue to attract outstanding trainees both at the graduate student and postdoctoral levels. Our clinical program remains strong even in these challenging times. We have introduced a new program with identified international affiliates to collaborate in our research. Most importantly, our faculty continue to make fundamental discoveries.

This year two of our faculty have received endowed chairs. Dr. Amita Sehgal was named the John Herr Musser Professor of Neuroscience and appointed Vice Chair of the Department of Neuroscience and Co-Director of the new Comprehensive Center for Neuroscience. Importantly, Amita was also elected as a member of the prestigious Institute of Medicine, one of the nation's highest honors in biomedicine. Dr. Sehgal has done groundbreaking studies identifying genetic pathways for the biological clock and for sleep regulation using Drosophila as a model organism.

Our colleague Dr. Terri Weaver also received an endowed chair—the Ellen and Robert Kapito Professor in Nursing Science—from the School of Nursing. Dr. Weaver is Chair of the Biobehavioral and Health Sciences Division in the School of Nursing. Dr. Weaver is internationally recognized for her work on functional consequences of sleep disorders and adherence to therapy. She has just completed, as Principal Investigator, a successful NIH-funded multicenter study on treatment of mild-to-moderate sleep apnea—the CATNAP study.

We, thus, currently at Penn have four faculty in sleep research with endowed chairs. In addition to Drs. Sehgal and Weaver, there is Joan Hendricks—the Gilbert S. Kahn Dean of Veterinary Medicine. Dr. Hendricks spent many years studying the physiology and anatomy of sleep in the English bulldog and now collaborates with other Center for Sleep faculty on the biochemical profile of rest and waking in flies. Last year, I had the honor of receiving an endowed professorship—The John Miclot Professor of Sleep Medicine. The National Sleep Foundation recently presented me with their Lifetime Achievement Award. I am grateful to them for this honor.

In the last year, even before the NIH Stimulus program, our research dollars grew by 20%. The ARRA has provided additional resources. It is particularly pleasing that our junior faculty received funds from the NIH Stimulus effort (Michael Brennick, Grace Pien and Nirinjini Naidoo).

One of the achievements in the last year that I find most gratifying is that the two winners of the Flexner Prize for the best neuroscience graduate student theses at Penn both did their thesis research in sleep. Christopher Vecsey, who worked in Ted Abel’s lab, recently published a paper in Nature (see Publications, p. 43) demonstrating the molecular mechanisms that underlie the impairment in hippocampal memory that occurs with sleep deprivation. Michael Halassa worked with Marcos Frank and Phil Haydon. They published a manuscript in Neuron (see Publications, p. 41) that showed that astrocytes play a critical role for signaling sleep homeostatic drive. This fundamental discovery will open a new area of investigation of sleep mechanisms.
international collaborations

Dr. Jini Naidoo works with visiting Norwegian students Renate Dysvik and Leni Grebstad.
Globalization has affected the medical research community much as it has the areas of economics, culture, politics and telecommunications. The Penn Center for Sleep has been involved in international collaborations for many years.

International collaboration was nurtured, in part, at the first International Sleep & Breathing Symposium held in Banff, Canada in 1989, with its major focus on the initial discoveries that were instrumental in the development of continuous positive airway pressure (CPAP) therapy, a method of treatment based on the notion that a mechanical expansion of the airway will help maintain airflow during sleep in the absence of upper airway muscle tone. Indeed, the origin of the Sleep & Breathing symposia dates further back to the Workshop on Respiratory Disorders of Sleep organized in 1986 by the National Heart, Lung and Blood Institute. In 2002, the International Sleep & Breathing Symposium was held in Reykjavik, Iceland. This was co-organized by Dr. Leszek Kubin (University of Pennsylvania) and Dr. Thorarinn Gislason (University of Iceland). Iceland is recognized as a country in which the genetics of complex disorders can be pursued with great efficiency thanks to the founder nature of the Icelandic population and the availability of extensive genealogical records. Consequently, there is broad expertise and extensive infrastructure for studies in population genetics, one of the areas of particular interest for studies of the sleep apnea syndrome and other sleep-related respiratory disorders.

The Center for Sleep has developed a strong collaboration with the University of Iceland (Drs. Thorarinn Gislason and Bryndis Benediktsdottir) and deCODE Genetics (Drs. Kari Stefansson and Ingileif Jonsdottir). We have assembled a very large cohort of patients with obstructive sleep apnea—the Icelandic Sleep Apnea Cohort (ISAC). This cohort of around 3,500 patients is being used for genetic studies (linkage, genome-wide association) and biomarker studies. Almost all recently diagnosed patients with obstructive sleep apnea (n=900) had biomarker assessments as well as abdominal and upper airway MRI. MRI data are analyzed at Penn by Dr. Richard Schwab's group.
We have also initiated a new study in Iceland looking at cardiovascular outcomes of treatment of sleep apnea (the Penn Iceland Sleep Apnea—PISA study) that is directed by Dr. Sam Kuna. This collaboration has been built on an R01 for genetic studies and the PISA study is part of a new program project grant. A PhD student in Iceland—Erna Arnardottir—is being jointly supervised by Drs. Gislason and Pack and spent a year at the University of Pennsylvania working on her thesis.

Other Center for Sleep scientists have collaborations with researchers around the globe. Dr. David Dinges, associate director of the Center, has ongoing collaborations with Drs. John Detre (Penn Neurology) and Mike Chee (Duke-National University of Singapore). Together, they work to identify the neural changes underlying the cognitive effects of sleep deprivation in healthy humans, using functional magnetic resonance imaging (fMRI) techniques. Joining them in these efforts are collaborators Dr. Hengyi Rao (Penn Psychiatry) and Dr. Dinges’ graduate student, Julian Lim, who also trained with Dr. Chee. Dr. Chee’s research with Dr. Dinges uses evoked fMRI to establish the effects of total sleep deprivation on working memory and sustained attention, and to identify imaging markers for individual differences in response to sleep deprivation. He has published his findings with Dr. Dinges in articles in *NeuroImage* and the *Journal of Neuroscience*.

This past year, Dr. Ning-Hung Chen visited the Penn Center for Sleep to learn in detail the research techniques that Drs. Schwab and Carole Marcus have utilized to understand the pathogenesis of sleep apnea. Dr. Chen is Director of the Sleep Center and Chief of the Department of Internal Medicine in the TaoYuang Branch of Chang Gung Memorial Hospital in Taiwan. He is also vice president of the Asian Society of Sleep Research. Dr. Chen spent three months at the Penn Sleep Center learning about upper airway imaging, Pcrit, airway morphometrics, and hypercapnic ventilatory responses. Drs. Schwab and Chen plan to collaborate on a study examining airway measurements in different ethnic populations (Asian, Caucasian, African-American) and in weight-matched controls and apneics.

Associate Professor of Psychiatry Michael Perlis collaborates extensively with University of Glasgow Professor Colin Espie. Director of the University of Glasgow’s Sleep Center, Professor Espie is an internationally renowned insomnia researcher. Together, he and Dr. Perlis are conducting a study funded by the NIH. The aim of the study is to explore the critical components of attentional processing in hopes of identifying a candidate marker for insomnia. Relatively little research has been undertaken to determine what precisely insomnia is and how it may confer risk for other disease states. The lack of research may be due in part to the fact that the insomnia phenotype lacks objective markers and that this is especially true for the phenomenon of cognitive arousal. To accomplish this, the Perlis/Espie study will use three domains of cognitive arousal to evaluate four groups: subjective mental experience (self report), performance (attentional processing) and cortical activity (qEEG). The primary
goals are to determine the extent to which the groups differ across these three cognitive domains, the component processes of attention most critical to this differentiation, and the relative predictive utility of each of the attentional measures. Subject recruitment is underway.

Children’s Hospital Sleep Center Director Carole Marcus is part of a research study that will take advantage of a unique cohort of ex-premature, 5-6 year old children who suffered apnea of prematurity, a common condition that is usually treated with methylxanthines. Methylxanthines are adenosine receptor blockers that have powerful influences on the central nervous system. However, little is known about the long-term effects of methylxanthines on the developing brain. In particular, it is not known whether methylxanthines have permanent adverse effects on sleep architecture and ventilatory control, resulting in an increased prevalence of sleep disorders such as insomnia and the obstructive sleep apnea syndrome (OSAS). Children who were born prematurely are at increased risk for neurobehavioral abnormalities. It is possible that these neurological comorbidities are mediated, in part, through sleep disturbances that may result from methylxanthine exposure. These children were randomized at birth to receive either caffeine or placebo, and are currently receiving detailed neurocognitive and behavioral assessments (the Caffeine for Apnea of Prematurity [CAP] trial). The cohort was originally part of a grant centered at McMaster University and Sunnybrook Health Science Centre in Toronto. Facilities in Australia, including Royal Women’s Hospital and Mercy Hospital for Women in Victoria, are also gathering data from subjects. These facilities are performing home sleep studies and all the data are gathered and analyzed by Dr. Marcus’ team here at CHOP. These studies will help determine the long-term consequences of neonatal methylxanthine therapy, ultimately resulting in improved management of apnea of prematurity.

Children’s Hospital Sleep Center Associate Director Jodi Mindell has been a member of the Asia Pacific Pediatric Sleep Association for several years. In 2008, she conducted a study on cross-cultural differences in infant and toddler sleep that looked at bedtimes, total sleep times and patterns of bed-sharing of Caucasian and Asian infants. Dr. Mindell found that there were vast differences in the two cultures and that Asian infants slept fewer hours, had later bedtimes, and had more perceived sleep problems with minimal differences in daytime sleep. There are many more questions to be answered, noted Dr. Mindell.
educational initiatives
Several members of the Center for Sleep direct or participate in a variety of educational initiatives within the Center, the University, both nationally and internationally.

Foremost, the Sleep Medicine Fellowship Program, now in its third year of ACGME accreditation, takes a multidisciplinary approach to training future physician-scientists and clinicians. The 12-month clinical fellowship is followed by two years (three if desired) of a research fellowship in sleep medicine. The length of our sleep fellowship is longer than needed to qualify for sleep medicine certification, but we are committed to providing a strong sleep-related research experience that prepares physicians for a career in academic medicine. The Center for Sleep serves as the research arm of the training program. Its nearly 50 faculty members are drawn from both clinical as well basic science departments, including Genetics and Neuroscience. Each fellow who elects to pursue formal research training forms a mentorship committee that provides advice and guidance during the training process.

Center members Drs. Michael Perlis and Philip Gehrman direct the Behavioral Sleep Medicine (BSM) program—one of only six in the nation approved by the American Academy of Sleep Medicine (AASM). The leadership of the Center for Sleep holds a strong belief in the importance of integrating psychological and behavioral approaches into the prevention and management of sleep disorders. In order to increase training opportunities in the burgeoning field of BSM, we have developed a training program that emphasizes these approaches to treatment. Available to clinical psychologists and other certified care providers, training in cognitive behavioral therapy for insomnia and other sleep-related disorders involves delivery of psychological interventions for these sleep disorders.

Dr. Richard Schwab, Professor of Medicine, has been directing the annual Advances in Diagnosis and Treatment of Sleep Apnea and Snoring course held on President’s Weekend at various national attractions, allowing attendees to bring their families to enjoy some time together. The course attracts 200-300 practitioners each year to learn about the latest novel treatments for snoring and sleep apnea including treatment approaches for obesity and sleep apnea, cardiovascular consequences of sleep apnea, palatal implants, new medical treatments for insomnia, and bariatric surgery.

For the first time, in 2010 the American Thoracic Society offered a new State of the Art (SOTA) course allowing participants to attend cutting edge lectures in Sleep. Dr. Richard Schwab is a course director for the Sleep State of the Art course that provides a comprehensive review of all aspects of sleep disorders including sleep apnea (new diagnostic and treatment strategies, cardiovascular consequences, complex sleep apnea, home sleep studies, economics, effects of bariatric surgery), consequences of sleep deprivation including immune function, narcolepsy, insomnia, parasomnias, restless leg syndrome and pediatric sleep disorders. State of the Art: Sleep provides didactic lectures from an outstanding group of faculty, PSG review sessions and case presentations.

The CPAP In-Service Educational Series, organized by Clinical Assistant Professor Maria Antoniou brings together representatives from the largest positive airway pressure (PAP) device companies with Center for Sleep health care providers, including medical assistants,
fellows, nurses, nurse practitioners and physicians to review the latest technical developments in PAP devices. These include CPAP, bilevel pressure, autoCPAP & bilevel and adaptive servo ventilation machines. The technical functioning of the devices are reviewed and criticized. Details regarding the machines’ compliance downloading functions are discussed and new interfaces are introduced and demonstrated.

The Polysomnogram (PSG) Lecture Series, held monthly, is geared primarily towards physicians, including rotating residents and fellows as well as fellows and physicians whose focus is solely on sleep medicine. Technical considerations specific to PSG interpretation are discussed and advances in PSGs, such as portable PSGs, are also reviewed. PSG interpretation specific to Pulmonary or Neurology subspecialization are also covered.

We have a very successful one-week Frontier course for final year medical students. The Medical School organizes a number of Frontier courses in the final months of medical school. These courses are intended to emphasize the interface between basic research and clinical practice. The sleep course attracts about 25 medical students and the entire week is dedicated to lectures and discussion groups about sleep and its disorders. Students break into groups, do a specific project and present their results on the last day of the course. It is a lot of fun for both students and faculty.

“Sleep: What is it, why do we need it, and how can we get more?” is a freshman seminar at Penn given by Lee J. Brooks, MD, Professor of Pediatrics. The globalization of society has placed increased demands on the human organism that was not designed to operate 24/7—particularly students. There are increased demands from school and work, and entertainment is easily available around the clock. The resulting sleepy society is a major public health problem that has contributed to motor vehicle accidents as well as disasters such as the Exxon Valdez and Chernobyl. Expertise from a sleep medicine physician teaches students that sleep is not unique to humans. All animals, from the mosquito to the cat, switch between phases of sleep and phases of activity. As the brain and neurological activity increased in complexity during evolution, so too did sleep. A trait that is conserved through these millions of years clearly has some special importance. In the course, Dr. Brooks explores the development and manifestations of sleep from the simple daily rest triggered by the biological clock in the fly to the complex brain wave changes in higher mammals, especially humans. Students study our own requirements for sleep, how it changes through the lifespan as we grow, mature, and age as well as the impact of sleeplessness on daytime performance.
Directed by nursing faculty Ann E. Rogers, PhD, RN, and Terri Weaver, PhD, RN, the graduate post-master’s certificate program in Sleep provides an inter-disciplinary, collaborative plan of coursework that prepares students to apply theoretical concepts of sleep for implementation in practice and research. The School of Nursing at Penn is a premiere institute in sleep research working collaboratively with the Center for Sleep and the Hospital of the University of Pennsylvania, the Philadelphia VA Medical Center, and Children’s Hospital. The program is designed to be flexible to allow for a combination of online courses and clinical experiences that will meet the needs of each student. The courses that are included have been developed based on the standards set by the AASM Training in Behavioral Sleep Medicine. The courses provide the student the opportunity to work collaboratively with other health care professionals in sleep medicine. The post-master’s certificate is academically rigorous focusing on research, education, and practice and trains students to practice sleep in the private and public health care sector, as well as in specialty units such as sleep laboratories. Students may use the courses to prepare for the AASM exam, as concentration courses in doctoral study and additional training in postdoctoral fellowship.

The Kids Judge! Neuroscience Fair was developed by faculty in the Biological Basis of Behavior program at Penn. Professor Ted Abel, along with colleagues from the Mahoney Institute of Neurological Sciences and the Center for Cognitive Neuroscience, designed a unique flip-flop of roles designed to make scientists better communicators and to interest elementary school students in science. The National Kids Judge! Neuroscience Fair Partnership is an education program designed to accomplish this. Universities and other institutions across the country organize and host this unique twist on the traditional science fair. The University of Pennsylvania hosted its first Kids Judge! Neuroscience Fair in March 2004. For each fair, the University plays host to children from local elementary schools. Biological Basis of Behavior majors conceive and build hands-on, fun-filled learning stations that draw the kid judges into activities that teach them how the brain and nervous system work.
fellowship training program

Dr. Ilene Rosen
As in all programs in the Center for Sleep, the Sleep Medicine Division’s fellowship training program has a strong multidisciplinary focus. The program has been accredited by the Accreditation Council for Graduate Medical Education (ACGME) and the AASM. Fellows are required to complete the 12-month ACGME clinical sleep medicine fellowship followed by two years (three if desired) of a postdoctoral research fellowship in sleep medicine. The length of our sleep fellowship is longer than needed to qualify for American Board of Medical Specialties certification, but we are committed to providing a strong sleep-related research experience that prepares physicians for a career in academic medicine.

The program accepts trainees who have completed training in Internal Medicine, Family Medicine, Neurology, Otolaryngology, Pediatrics, Psychiatry and Pulmonary Medicine. Recent trainees in the fellowship program completed residency training in Pulmonary (6), Neurology (3), Psychiatry (1), Internal Medicine (1), and Pediatrics (2).

Located within the Department of Medicine, the Sleep Division has 13 full-time faculty members. Staff at the clinical and research sleep laboratories at three adjacent hospitals—Hospital of the University of Pennsylvania (HUP), the Children’s Hospital of Philadelphia (CHOP), and the Philadelphia Veterans’ Affairs Medical Center (VA)—evaluate patients with a full range of sleep disorders. The Center for Sleep serves as the research arm of the training program. With nearly 50 faculty members, they are drawn from the clinical departments mentioned above as well as basic science departments. Each fellow forms a mentorship committee that provides advice and guidance during the training process. Given the multidisciplinary structure of the program, the fellowship curriculum is tailored to allow each trainee to concentrate on his/her particular area of specialization. After the 2009 certification exam in Sleep Medicine, the division enjoyed a 100% pass rate.

The first year of the fellowship is a dedicated clinical training program that functions in collaboration with CHOP. Thus, we train both adult and pediatric sleep medicine physicians. The program is thriving under the leadership of Program Director Ilene Rosen, MD, MSCE, and Associate Program Director, Alex Mason, MD, PhD, MSCE. It is a comprehensive one-year program that consists of two tracks, an adult and a pediatric sleep medicine track. We are also committed to training physician-scientists. Thus, we seek applicants who have this goal and anticipate that fellows interested in research training in sleep medicine will spend three years in our program—one clinical year and at least two years in research. Fellows see adult patients at our clinical facility at 3624 Market Street, our community-based outpatient facilities, Penn Medicine at Radnor and Cherry Hill, and the Sleep Center at the Philadelphia VA under the direction of Dr. Sam Kuna. Pediatric patients are evaluated by fellows at the Sleep Center at CHOP. Fellows perform inpatient consultations at both HUP and CHOP.

We are also working with our colleagues in Pulmonary and Critical Care Medicine to develop a new combined Pulmonary/Sleep Medicine fellowship program. This will, we believe, fill an important national need.

Our comprehensive Sleep Medicine Lecture Series, held primarily in the summer months, covers all aspects of sleep medicine. During the rest of the year we have a weekly Clinical Case Conference (case presentation followed by presentation of latest information on the topic). Two Research-in-Progress Conferences and Sleep Medicine Journal Clubs are also held monthly. Our state-of-the-art video conferencing system allows other sleep medicine programs to join our educational activities. This step helps us to meet our goal of being a Regional Comprehensive Interdisciplinary Sleep Center.
basic science research

Dr. Sigrid Veasey and Dr. Yan Zhu
The scientist members of the Center for Sleep continue to make important discoveries in the understanding of the molecular mechanisms regulating sleep and wakefulness.

Howard Hughes Medical Investigator Amita Sehgal’s work in Drosophila continued with publication in the Journal of Neuroscience last year of a study showing that caffeine promotes wakefulness in the fly in part by inhibiting cAMP phosphodiesterase activity. Another study on the previously discovered SLEEPLESS gene appeared in Nature Neuroscience.

Marcos Frank, PhD, in Neuroscience, is currently focused on the cellular basis of sleep function and homeostasis. His lab is investigating the role of sleep in a canonical form of plasticity in vivo known as ocular dominance plasticity (ODP). The findings are that sleep is necessary for the consolidation of ODP and this process involves NMDA receptor and kinase activation in the sleeping brain. With his colleague, post doctoral fellow Sara Aton, they have reported findings that support the hypothesis that a key function of sleep is the consolidation of waking experience. They published a report in Neuron that shows for the first time, how cellular changes in the sleeping brain promote the formation of memories.

Post doctoral student Chris Vecsey of the Neuroscience Graduate Group under the mentorship of Biologist Ted Abel, demonstrated that even brief sleep deprivation causes disruption of hippocampal function producing memory deficits. Their study appeared in Nature.

Dr. Pack continues his program in studying the molecular mechanisms of sleepiness and sleep promotion. Changes in sleep promoting mechanisms with age are examined by Drs. Pack, Abel, Sehgal, and Nirinjini Naidoo as part of a program project on “The Mechanisms of Alterations in Sleep with Age.” Dr. Naidoo published a study providing new evidence that modest sleep deprivation in aging induces cellular stress. Understanding the pathways activated by sleep loss and the mechanisms by which they occur will allow the development of therapies to protect the brain in sleep disorders including those associated with aging.

Dr. Sigrid Veasey has developed a major program of research on oxidative injury to neurons in models of obstructive sleep apnea (OSA), work that is ready for clinical translation.

Assistant Professor David Raizen continues his work in studying the sleep-like state called lethargus in the worm, having already shown that lethargus has several similarities to sleep including reversibility, increased sensory arousal threshold, and homeostasis, manifested by a decreased latency to sleep and an increased depth of sleep following a period of deprivation.

Dr. Leszek Kubin of the School of Veterinary Medicine has an active program of research studying the neurochemistry, neuroanatomy and neurophysiology of the effects of rapid eye movement (REM) sleep on the neural control of upper airway muscles using a rodent-based, pharmacological model of sleep.

By examining the relevance of these findings across different species, investigators at Penn have the ability to identify evolutionary conserved molecules regulating sleep.
patient-oriented research

Dr. Richard Schwab and Research Specialist Matthew Thorne-FitzGerald.
The Center for Sleep has an extensive program of patient-oriented research and a major commitment to this area. Indeed in 2009, we were awarded funding for a program project entitled “Endophenotypes of Sleep Apnea and Role of Obesity” designed to distinguish the relative importance of obstructive sleep apnea (OSA) and obesity in causing their shared functional, metabolic and cardiovascular consequences. Both obesity and sleep apnea are felt to increase the risk of diabetes, hypertension, and cardiovascular disease. The proposed research will begin to determine if treating obese patients with sleep apnea helps to reduce these risks.

Other programs in the Sleep Medicine Division include Dr. Grace Pien’s study on the development of sleep apnea with menopause and Dr. Indira Gurubhagavatula’s study screening for sleep apnea in commercial drivers.

In Psychiatry, Drs. Michael Perlis and Philip Gehrman have an ongoing study on insomnia in cancer patients. Faculty in Nursing Science also have a robust research program described in detail elsewhere in this report by Dr. Terri Weaver, Chair of the Biobehavioral and Health Science Division in the School of Nursing.

Our cores help support this. The Research Sleep Core, has both adult and pediatric components. These are supported as part of the Center for Translational Science Award (CTSA). On the adult side, there are four bedrooms dedicated for sleep research and on the pediatric sleep center, two bedrooms. These facilities are managed by experienced staff that provide a broad range of studies: overnight sleep studies; multiple sleep latency and maintenance of wakefulness tests; actigraphy; neurobehavioral tests of function. These facilities are available to all faculty at Penn and Children’s Hospital who have an interest in sleep research. This approach has greatly facilitated our development of a vibrant program of research in this area.

Dr. Sam Kuna runs a core for centralized scoring of sleep studies from multiple locations. This facility is being used for two NIH-funded multicenter studies: CPAP (continuous positive airway pressure) Apnea Trial – North American Program (CATNAP), assessing outcomes of therapy with CPAP in patients with mild-to-moderate sleep apnea who are excessively sleepy; and Sleep Action for Health in Diabetes (Sleep AHEAD) evaluating prevalence of OSA in obese Type 2 diabetics, progression of disease and effects of behaviorally induced weight loss.

Dr. Richard Schwab has developed an upper airway imaging core to facilitate analysis of three-dimensional images of the upper airway, surrounding soft tissues and craniofacial structure. This core is being used for studies in adults (Dr. Schwab) and in children (Dr. Marcus). It is also being used to analyze MR images collected in Iceland as part of our ongoing study of genetics of sleep apnea (Dr. T. Gislason, Dr. A. Pack, and deCODE Genetics). Currently, we have funded programs of research in several distinct areas. Tools developed at the University of Pennsylvania such as the Multivariable Apnea Prediction (Maislin et al, Sleep 18:158-166, 1995) and Functional Outcomes of Sleepiness Questionnaire (Weaver et al, Sleep 20:835-843, 1997) are now used in patient-oriented research around the world and have been translated into many languages.

Finally, important new initiatives in patient-oriented research have recently been developed. First, we are building a program of research in the cardiovascular consequences of sleep apnea. We have funding to study the relative role of obesity and OSA in the inflammatory state. Second, under the direction of Dr. Sam Kuna, we are developing a new program in Health Care Delivery Research in OSA. This effort is based at the Sleep Center at the VA Medical Center. Third, we are aggressively pursuing development of research programs in the genetics of sleep and its disorders, under the direction of Dr. Pack.
Megin Myers, CRNP and Dr. Luqi Chi.

clinical program
We have worked over the past year to further refine the practice of clinical sleep medicine at Penn. Comprehensive care for the full spectrum of sleep disorders is provided by our multidisciplinary team which includes individuals with primary training in pulmonary medicine, neurology, psychiatry, internal medicine, pediatrics, clinical psychology and nursing.

In keeping with the pattern of yearly growth we have seen since the Division of Sleep Medicine was established in the Department of Medicine in 2001, there has been an increase in patient visits in fiscal year 2009. More than 8500 outpatient evaluations were performed, including both new and returning patients, a 23% increase over the preceding year.

Among the factors contributing to this sizable growth are our CPAP follow-up program led by Dr. Sharon Schutte-Rodin, and our program in Behavioral Sleep Medicine, led by Dr. Michael Perlis and clinical director Dr. Philip Gehrman.

The CPAP follow-up program includes on-site assistance with CPAP equipment, regular monitoring of patient adherence and CPAP efficacy, and expert support from Andrea Bergmann, RN and Megin Myers, CRNP.

The Behavioral Sleep Medicine program has offered therapy to an increasing number of patients as the effectiveness of cognitive behavioral therapy for insomnia has become widely recognized. Dr. James Findley, a clinical psychologist with a broad background in sleep medicine, has joined Dr. Gehrman in providing these services and enabled us to open an insomnia clinic at Penn Medicine at Radnor in addition to our site on Penn’s campus.

We have also expanded our general clinical services to two new sites, French Creek near Phoenixville, PA, and Cherry Hill, NJ, where Dr. Ilene Rosen has established a growing practice.

We have added three physicians to our faculty: Dr. Ron Anafi, who has a background in pulmonary mechanics, Dr. Subhajit Chakravorty, whose primary field is psychiatry; and Dr. Dafia Ofer, a pediatrician who has trained in both adult and pediatric sleep medicine. Each of these physicians is a graduate of the Penn Sleep Medicine Fellowship program.

We continue to perform more than 5000 sleep studies per year in total at our three Philadelphia and two suburban sleep laboratory facilities, using state of the art equipment. Our laboratory facilities are supported by increasingly complex information management technology which serves both our clinical and research needs.

Together our outpatient clinics and sleep laboratories enable us to maintain our commitment to excellence in clinical care, clinical research and education for trainees in sleep medicine.

“...the effectiveness of cognitive behavioral therapy for insomnia has become widely recognized.”

Charles Cantor, MD, Director
the sleep program at the children's hospital of Philadelphia
The mission of the Sleep Center at the Children’s Hospital of Philadelphia (CHOP) is to provide comprehensive diagnostic evaluation and management to pediatric patients of all ages, using a family-centered approach; to provide education for medical and psychological trainees and practitioners, patients and the general community; and to develop research to lead to a better understanding of normal and abnormal sleep during childhood and development. The Sleep Center at CHOP continues to be highly productive in both the clinical and research arenas.

The American Academy of Sleep Medicine-accredited Sleep Center comprises the Sleep Clinic, Sleep Laboratory, and research program. The faculty includes Drs. Marcus, Suzanne Beck and Lee Brooks (pediatric pulmonology), Drs. Alex Mason and Lawrence Brown (pediatric neurology), Drs. Jodi Mindell and Lisa Meltzer (psychology) and Dr. Jingtao Huang (research). Dr. Ignacio Tapia (pediatric pulmonology), who received his training at CHOP, joined the faculty in December 2009. The Center also includes pediatric sleep fellows, who participate in a joint training program with the University of Pennsylvania, and two dedicated sleep nurses (Heidi Johnson and Mary Kate Menello).

The interdisciplinary pediatric Sleep Clinic evaluates children with a wide range of sleep disorders including sleep-disordered breathing, narcolepsy, restless legs syndrome, parasomnias, insomnia and behavioral problems.

The Sleep Laboratory has 6 beds. Under the leadership of Clinical Laboratory Supervisor Brian Schultz, and Sleep Laboratory Medical Director Suzanne Beck, sleep studies have increased to approximately 2,000 per year.

Ongoing research in the CHOP Sleep Center includes NIH-funded studies (R01’s, U01 and K23’s) on the pathophysiology of childhood obstructive sleep apnea (Dr. Marcus); oxyhemoglobin desaturation and vasculopathy in sickle cell disease (Drs. Mason and Marcus); long-term effects of therapeutic caffeine use for apnea of prematurity on sleep disorders (Drs. Marcus and Meltzer), pediatric obstructive sleep apnea and the metabolic syndrome (Drs. Kelly, Katz and Brooks); and sleep, depression and psychosocial risk factors in caregivers of children with chronic disease (Dr. Meltzer). In addition, CHOP is one of the centers for an NIH-funded, randomized, clinical trial evaluating the efficacy of adenotonsillectomy for childhood sleep apnea (the CHAT study). Other studies being conducted in the Sleep Center include an American Heart Association-funded study on respiratory-related evoked potentials in children with obstructive sleep apnea (Dr. Huang), studies evaluating the effects of CPAP in children (Drs. Marcus and Meltzer and nurse practitioner Natalie Difeo), studies of chronic pain and fatigue in children (Drs. Sherry and Brooks), the prevalence of pediatric sleep disorders in primary care (Drs. Meltzer and Mindell), sleep patterns and maternal stress in infants with congenital heart disease (Dr. Meltzer), and cultural differences in sleep patterns in infancy (Dr. Mindell).

The CHOP sleep faculty members continue to maintain a strong national leadership role. Some of their new responsibilities include: Dr. Brown is president of the Child Neurology Foundation, as well as a member of the American Academy of Pediatrics Subcommittee on attention deficit hyperactivity disorder. Dr. Brooks is President of the New Jersey
The interdisciplinary pediatric Sleep Clinic evaluates children with a wide range of sleep disorders.”

Dr. Jodi Mindell.

Sleep Society. Dr. Marcus is chairing a committee to revise the American Academy of Pediatrics guidelines on childhood obstructive sleep apnea, and an American Academy of Sleep Medicine committee on guidelines for indications for pediatric polysomnography. Dr. Marcus co-chaired NIH meetings on Developmental Aspects of the Upper Airway and Pediatric Drug & Medical Device Development, and chaired an NIH study section.

CHOP faculty are on the editorial boards for a number of academic publications. Dr. Marcus continues to be a deputy editor for the journal SLEEP, and Dr. Mindell is on the SLEEP editorial board. Faculty members are on the editorial boards of Behavioral Sleep Medicine (Dr. Meltzer, Dr. Mindell), the Journal of Pediatric Psychology (Dr. Meltzer), Chest (Dr. Marcus) and Paediatric Respiratory Reviews (Dr. Marcus). Dr. Brooks continues his course for undergraduates at the University of Pennsylvania, entitled “Sleep: What is it, why do we need it, and how to get more.” The Sleep Center continued to educate foreign physicians in pediatric sleep medicine, including long-term visitors from Hong Kong, Taiwan, India and Spain.

The Sleep Center faculty and fellows published 9 peer-reviewed manuscripts in the past year, in journals such as The American Journal of Respiratory and Critical Care Medicine, Sleep, Behavioral Sleep Medicine, Journal of Clinical Psychology and the Journal of Pediatric Psychology. In addition, they published numerous book chapters, reviews and editorials. Dr. Mindell also published the second edition of Clinical Guide to Pediatric Sleep (Lippincott Williams & Wilkins), co-authored with Dr. Judith Owens.

CHOP faculty and fellows participated in numerous scientific and educational presentations at national conferences including SLEEP 2009, where they presented a total of 13 abstracts.

Dr. Jodi Mindell.

Dr. Meltzer received the Investigator Award from the American Academy of Sleep Medicine Child Sleep Disorders and Development Section. Dr. Mindell was co-chair of the Fifth Annual Pediatric Sleep Medicine Conference. Sleep Center faculty gave many invited talks, including international lectures in Austria (Dr. Suzanne Beck); China, Vietnam and Japan (Dr. Mindell); and Belgium, Taiwan and Korea (Dr. Marcus).
sleep and chronobiology research in the department of psychiatry

Drs. Michael Perlis and Phil Gehrman
Faculty in the Unit for Experimental Psychiatry, Division of Sleep and Chronobiology continue to make important discoveries regarding the nature of and dynamic changes in human physiological and neurobehavioral responses produced by acute and chronic partial sleep loss.

Dr. Dinges’ laboratory, which includes Dr. Namni Goel and Dr. Mathias Basner, has demonstrated that healthy adults undergoing total sleep deprivation (TSD) showed trait-like (phenotypic) differential vulnerability in their neurobehavioral responses to sleep loss. Such differential vulnerability also has been documented in chronic partial sleep deprivation (PSD) conditions, in which sleep is restricted to 4-6.5h time in bed per night. These findings have resulted in a search for possible candidate genes that may underlie these phenotypic responses. Recently, Dr. Dinges, his colleagues, Drs. Namni Goel and Siobhan Banks, and their genetics collaborator, Dr. Emmanuel Mignot (Stanford University) published a paper in PLoS One showing that the variable number tandem repeat (VNTR) polymorphism 5-repeat allele of the circadian gene PERIOD3 (PER3^{5\text{r}}), which has been associated with increased cognitive deficits to a night of TSD relative to the 4-repeat allele (PER3^{4\text{r}}), was not associated with individual differences in neurobehavioral responses to PSD.

These investigators have also published a review in Seminars in Neurology on the cognitive functions affected by sleep loss including psychomotor and cognitive speed, vigilant and executive attention, working memory, and higher cognitive abilities. This group pioneered the largest chronic sleep-restriction experiments conducted to date – which model the kind of sleep loss experienced by many individuals with sleep fragmentation and premature sleep curtailment due to disorders and lifestyle. These studies, which have involved more than 350 healthy adults have demonstrated that cognitive deficits from sleep restriction accumulate to severe levels over time without full awareness by the affected individual. They have also used functional neuroimaging to reveal that frequent and progressively longer cognitive lapses, which are a hallmark of sleep deprivation, involve distributed changes in brain regions including frontal and parietal control areas, secondary sensory processing areas, and thalamic areas. The robust differences among individuals in their cognitive vulnerability to sleep loss may have a basis in genes regulating sleep homeostasis and circadian rhythms.

In a collaborative effort with colleagues from Washington State University and Pulsar Informatics, data from experiments in the Dinges lab have been used to develop computational models and to improve mathematical models of performance and alertness in three key areas: (1) more accurate prediction of the effects of chronic sleep restriction on performance; (2) improved prediction of the dynamics of recovery
from, and recycle back into sleep restriction; and (3) enhanced prediction that takes into account individuals differences in performance vulnerability to chronic sleep loss. A paper recently published in the *Journal of Theoretical Biology* (McCauley et al., 2009) revealed that the 2-process model belongs to a broader class of models formulated in terms of coupled non-homogeneous first-order ordinary differential equations, which have a dynamic repertoire capturing waking neurobehavioral functions across a wide range of wake/sleep schedules.

Dr. Hengyi Rao, Dr. John Detre, and graduate student Julian Lim have used arterial spin labeled perfusion fMRI—an absolute measure of blood flow developed by Dr. Detre and colleagues—to evaluate the neural correlates of performance on Dr. Dinges’ Psychomotor Vigilance Test (PVT) in both alert and sleep-deprived adults; to identify changes in neural regulation with time-on-task fatigue; and to find biomarkers for phenotypic differential vulnerability to sleep deprivation. Under this mentorship, Julian Lim continues to produce excellent work. In 2008, he won the award for best presentation in clinical/translational research at the annual Center for Sleep Research Retreat for his work in this area. The unique capabilities of Dr. Dinges’ laboratory include the the ability to experimentally study healthy adult volunteers for up to 21 consecutive days in a specially equipped, environmentally isolated Sleep and Chronobiology Laboratory and in the NIH Clinical and Translational Research Center at HUP. Basic human translational research within the laboratory characterizes the relationship between the biological basis of sleep need and circadian physiology (e.g., genetics, brain imaging, psychopharmacology), and their control of waking neurobehavioral functions and health, as reflected in mood, physiological alertness, a range of cognitive functions, quantitative EEG/EOG, endocrine, immune, and inflammatory responses. The laboratory also evaluates neurobehavioral functioning in response to stress and collaborates in studies of pathologies of sleep and wakefulness (e.g., circadian sleep disorders, hypersomnolence syndromes, insomnias, and insufficient sleep syndromes). In addition to basic human laboratory research, the Unit conducts and collaborates in the following areas: (1) population science on sleep-wake behaviors; (2) development of biomathematical and computational models of sleep and circadian effects on behavior; (3) studies of sleep and performance in simulators and analog environments (e.g., NEEMO); (4) studies of sleep and performance in operational environments (e.g., truckers, commercial flight crews, astronauts on the International Space Station); and (5) neurobehavioral technology development for use in clinical trials and field studies of occupational fatigue.

Dr. Michael Perlis has been doing research on sleep disorders for more than 20 years. He focuses primarily on insomnia including the neurocognitive phenomena in insomnia, the mechanisms of action of sedative hypnotics, and the development of alternative treatments for insomnia. Currently, he is working with University of Glasgow Professor Colin Espie. They are conducting a study funded by the NIH to explore the critical components of attentional processing to possibly identify a candidate marker for insomnia. Relatively little research has been undertaken to determine what precisely insomnia is and how insomnia may confer risk for other disease states. This may be due, in part, to the fact that the insomnia phenotype lacks objective markers; this is especially true for the phenomenon of cognitive arousal. To accomplish this, three domains of cognitive arousal will be evaluated in four groups: subjective mental experience (self report), performance (attentional processing) and cortical activity (qEEG). The primary goals will be to determine the extent to which the groups differ across these three cognitive domains, the component processes of attention most critical to this differentiation, and the relative predictive utility of each of the attentional measures.

Dr. Perlis also holds an R01 to study the so-called "placebo effect" particularly regarding treatment of insomnia. Subjects with primary insomnia will be
treated with medication for a period of one month and then randomized to one of four groups for a period of 12 weeks; one receiving full-dose medication on a nightly basis, one receiving full-dose medication on 14 of 28 nights where placebo is provided on non-drug nights, one receiving full dose medication on 14 of 28 nights where no pills are taken on non-drug nights, and one receiving diminished dose medication on a nightly basis. The value of the proposed research resides in its capacity to provide for the long term treatment of insomnia in a manner that increases the durability of pharmacotherapy while reducing the overall amount of medication required. If proven effective in the current application, this new approach to pharmacotherapy and placebo effects is likely to stimulate new interdisciplinary research for the treatment of a variety of chronic diseases. Dr. Perlis also conducts studies to compare the effectiveness of cognitive behavioral therapy for insomnia (CBT-I) with medication. He directs the Behavioral Sleep Medicine program at Penn which provides CBT-I to patients with intractable insomnia.

At the Philadelphia Veteran’s Affairs Medical Center, Professor of Psychiatry Richard Ross is studying the effects of psychological stress on sleep. Dr. Ross is a member of the Post Traumatic Stress Disorder (PTSD) Clinical Team in the Behavioral Health Service at the VA. He treats veterans with PTSD. In his clinical research, Dr. Ross is studying the effectiveness of imagery rehearsal, a form of cognitive behavioral therapy, for the sleep and nightmare disturbance in PTSD. Together with Dr. Adrian Morrison of the School of Veterinary Medicine, they are studying the effects of psychological stress on sleep in rats, including a strain known to be highly reactive to stress. Dr. Ross also collaborates with Dr. Leszek Kubin in studies of the hypothalamic control of sleep in rats and with Dr. Philip Gehrman in studies of primary insomnia in humans.

The overarching goal of research in sleep in the Department of Psychiatry is to discover new ways to effectively detect, prevent and treat neurobehavioral and physiological impairments from sleep loss and related stressors, their adverse effects on health, behavior, and safety using novel behavioral, pharmacological and technological countermeasures.
sleep research in the school of nursing
The University of Pennsylvania School of Nursing has one of the largest concentrations of nurses studying sleep in the country. Dr. Terri Weaver, the first nurse researcher at Penn to study sleep, recruited Dr. Ann E. Rogers in 1998, and Dr. Norma Cuellar a few years later. Dr. Kathy Richards, Diplomate, American Board of Sleep Medicine, was recruited from the University of Arkansas where she was Associate Chief Nurse, Research, VA Medical Center. Dr. Richards’ research is in the area of sleep disruption and cognition in older adults, particularly those with mild cognitive impairment.

Drs. Barbara Riegel and Nancy Tkacs have begun studying sleep in their populations of interest – patients with congestive heart failure and diabetes. Post doctoral students, supervised by Drs. Rogers and Weaver, are investigating topics ranging from sleep in HIV-positive patients and patients with lung cancer, to sleep and obesity in pediatric patients, as well as sleep in patients with COPD or diabetes mellitus. Drs. Valerie Rogers and Margaret Souders are the newest post doctoral fellows in Nursing. Dr. Valerie Rogers’ research is in the area of sickle cell disease and sleep in children and Dr. Souders has investigated sleep in autism. Faculty research is also wide-ranging, with projects focusing on the management of sleep disorders, sleep in other medical disorders, and the effects of staff nurse fatigue on patient safety.

Ongoing research projects include Dr. Weaver’s investigation of residual sleepiness in adherent CPAP patients including whether neuronal damage documented by PET scan is a potential factor and Dr. Cuellar’s funded research focuses on the impact of restless leg syndrome (RLS) on quality of life. In addition to documenting the high prevalence of RLS among diabetic patients, she is conducting a randomized control trial evaluating the efficacy of valerian for the management of RLS. Finally, Dr. Ann E. Rogers’ newest funded project is focused on evaluating the efficacy of adding a sleep extension protocol to a diet and exercise program to promote weight loss in obese adults.
Al...
Lawrence W. Brown, MD
Associate Professor of Neurology and Pediatrics; Co-Director, Pediatric Neuropsychiatry Program
Dr. Brown is interested in the interaction of sleep and neurological disease in children. There are several model areas of clinical interest, particularly the effects of sleep disorders and disturbances of the sleep-wake cycle in epilepsy and ADHD. Childhood epilepsy has important effects on alertness, attention and behavior. Some seizure and epilepsy syndromes are seen primarily in drowsiness or sleep; these may mimic primary sleep disorders like parasomnias. Sleep resistance, sleep-onset insomnia and poorly consolidated sleep are more commonly found in children with ADHD than control populations. Obstructive sleep apnea and periodic leg movements of sleep are often under-recognized but treatable causes of hyperactivity and inattentiveness. Similarly, other childhood neurological disorders (i.e., Tourette syndrome, autism, mental retardation, Prader-Willi syndrome, Smith-Magenis syndrome, etc.) have important interactions with sleep through primary disturbances of sleep, drug interactions and other mechanisms. Dr. Brown’s lab is developing collaborations to investigate aspects of sleep in these special pediatric populations.

Maja Bucan, PhD
Professor of Genetics; Chair, Genomics and Computational Biology Graduate Group
Dr. Bucan’s laboratory studies the genetic basis of behavioral and psychiatric disorders. To complement ongoing efforts in human psychiatric genetics, her laboratory has embarked over the last several years on two major projects: a screen for novel behavioral mutations in the mouse and the functional annotation of the mammalian genome using bioinformatics approaches. Current focus is on the identification of endophenotypes – biochemical, physiological or behavioral components of a clinical syndrome. The goal of the behavioral screen is to identify mouse mutants that can serve as animal models for human psychiatric disorders or more specifically, to identify genes/SNPs (single nucleotide polymorphism) known to cause behavioral anomalies in mice and then use them as candidate genes in human genetics.

Charles Cantor, MD
Clinical Associate Professor of Neurology and Medicine; Medical Director, Penn Sleep Centers
Dr. Cantor oversees the clinical program of the Penn Sleep Centers which has outpatient practice sites at 3624 Market Street and Penn Medicine at Radnor, as well as sleep laboratory facilities in three University City locations, and in Audubon and Doylestown, PA. His clinical interests include sleep disturbances in Parkinson’s disease and other extrapyramidal disorders, narcolepsy, adult parasomnias, and restless legs syndrome (RLS). He is currently participating in clinical research on sleep quality in Parkinson’s disease and the effects of gastric bypass surgery on obstructive sleep apnea. He is collaborating in these studies with colleagues in the Movement Disorders Center and in the Bariatric Surgery Program at Penn.

Subhajit Chakravorty, MBBS
Clinical Associate in Sleep and Psychiatry
Dr. Chakravorty is board certified in sleep medicine, a staff psychiatrist at the Addiction Recovery Unit of the Philadelphia Veterans Affairs Medical Center, and an investigator for the VA’s Mental Illness Research Educational and Clinical Center (MIRECC). He specializes in the care of patients with sleep disorders and associated substance abuse and/or mental illness. He recently presented his findings on the predictors of sleep quality in actively drinking veterans at the VA National Mental Health Conference in Washington, DC. His current research is on the effect of the drug quetiapine, as compared to placebo, on the sleep of veterans recovering from alcoholism. He is also a co-investigator on a project investigating the sleep and metabolic effects of night eating in the context of other eating disorders.

Diego Contreras, PhD
Associate Professor of Neuroscience
The focus of Dr. Contreras’ lab is the generation and synchronization of rhythms that characterize the waking and sleep states as well as the transition from certain sleep patterns into seizure activity. Using intracellular and optical recordings in vivo, they address questions concerning the cellular mechanisms of rhythm generation in cerebral cortex and thalamus. Using genetically modified mice, they try to understand the role of particular ionic channels expressed in specific populations of cortical and thalamic cells for their transition into epileptic patterns.
Norma Cuellar, DSN, RN
Assistant Professor of Nursing
Dr. Cuellar's research focuses on the use of Complementary and Alternative Medicine (CAM) in patients with sleep problems, specifically restless legs syndrome (RLS). Since RLS is often not correctly diagnosed until older age, her focus is on gerontological perspectives of both CAM and RLS. Two studies are currently underway. The first looks at older adults and compares symptoms of primary and secondary RLS. The second project examines the prevalence of RLS in type 2 diabetics and outcomes of sleep and glycemic control. Dr. Cuellar also studies the use of valerian on sleep in persons with RLS.

David F. Dinges, PhD
Professor of Psychology; Director, Unit for Experimental Psychiatry, Division of Sleep and Chronobiology, Department of Psychiatry
The primary focus of Dr. Dinges' research is on identifying the manner in which sleep and the endogenous circadian pacemaker interact to control wakefulness and waking neurobehavioral and physiological functions. Laboratory experiments are directed at the dual goals of establishing the nature of the physiological and neurobehavioral changes engendered by sleep loss and circadian rhythmicity, and testing the effectiveness of countermeasures to these changes. Current research areas include experimentally identifying the effects of chronic sleep loss on neurocognitive functions and physiological profiles; determining the essential physiological features of recovery sleep; and evaluation of novel behavioral, technological and pharmacological countermeasures to sleep deprivation and circadian rhythm disturbances.

Marcos Frank, PhD
Associate Professor of Neuroscience
Research in the Frank laboratory is currently focused on the cellular basis of sleep function and homeostasis. They are investigating the former by examining the role of sleep in a canonical form of plasticity in vivo known as ocular dominance plasticity (ODP). Their findings are that sleep is necessary for the consolidation of ODP and this process involves NMDA receptor and kinase activation in the sleeping brain. They have also discovered that this type of sleep-dependent plasticity is profoundly altered by specific hypnotic drugs and may require T-type calcium channels. They are investigating the latter by examining the role of astrocytes in sleep homeostasis. They have found that astrocytes are key cells in the accumulation and discharge of sleep need in the mammalian brain.

Richard O. Davies, DVM, PhD
Professor of Physiology, School of Veterinary Medicine
Current investigations center on the neural mechanisms underlying the obstructive apneas/hypopneas that occur during sleep, especially rapid eye movement (REM) sleep. For this, animal models of REM sleep are used to study the changes in the control of motoneuronal activity to various respiratory muscles (both upper airway and respiratory pump muscles) that accompany REM sleep. A REM sleep-like state is induced bringing about a profound suppression of activity in motoneurons to most respiratory muscles. There is a differential suppression of respiratory motoneuronal activity, with a pattern similar to natural REM sleep. The role of the two aminergic systems of the brainstem in the motor and reflex control of upper airway motoneurons (hypoglossal, pharyngeal, laryngeal) and the relation of these systems to the atonia of REM sleep is currently being investigated using a variety of complementary neurophysiological, neuroanatomical and neuropharmacological techniques.

Eliot Friedman, MD
Instructor in Medicine, Division of Sleep Medicine
Dr. Friedman works with Dr. Amita Sehgal using the fruit fly genetic model system. His work is focused on two tracks: The first is to understand the genetic underpinnings of the variability in symptom severity among patients with obstructive sleep apnea. For this he uses a model of severe intermittent hypoxia delivered at night. His studies have shown that following this exposure flies, much like humans, exhibited a daytime sleepiness phenotype. The second track involves a collaboration with Dr. Max Kelz in which flies are administered volatile anesthetics to explore the neuronal circuits that mediate their arousal from anesthesia. Together, Drs. Friedman and Kelz have successfully established an anesthetic paradigm in flies using cessation of locomotor behavior as an endpoint. Given that arousal from the anesthesia will likely share many characteristics with endogenous arousal from the sleep state they believe that this line of research will help understand the regulation of the state transitions between normal wake and sleep.
Philip Gehrman, PhD
Assistant Professor, Department of Psychiatry

Dr. Gehrman’s research focuses on the pathophysiology and treatment of insomnia. Currently, he is investigating how insomnia may relate to excessive reactivity of the stress response system. Future studies will focus on the underlying brain mechanisms of insomnia as well as work towards identifying genes related to the disorder. He conducts clinical studies examining strategies for improving both cognitive behavioral and pharmacologic treatments of insomnia. Dr. Gehrman is clinical director of the Behavioral Sleep Medicine program for the Center for Sleep, which involves delivery of psychological interventions for sleep disorders. He has also developed a new behavioral sleep medicine training program to train clinical psychologists in cognitive behavioral therapy for insomnia and other stress-related disorders.

Namni Goel, PhD
Research Assistant Professor of Psychology in Psychiatry, Division of Sleep and Chronobiology, Department of Psychiatry

Dr. Goel’s research investigates how physiological, behavioral and environmental factors affect sleep, circadian rhythms and regulate mood. Through a multidisciplinary approach - bridging clinical and biological psychology, psychiatry and behavioral neuroscience - Dr. Goel has shown that environmental, non-drug stimuli substantially alter sleep and mood and modify circadian rhythms in clinical and nonclinical populations. She has pursued these interests in two related research lines: sleep, circadian rhythm, and mood regulation in response to light and other environmental stimuli in humans and in a diurnal rodent; and the etiology, definition and measurement, and treatment of seasonal affective disorder (SAD) and nonseasonal depression. Dr. Goel has obtained funding from NIA and NIMH, as well as a grant from a private foundation (Sense of Smell Institute) for her research.

Lee Goldberg, MD, MPH
Associate Professor of Medicine, Division of Cardiovascular Medicine; Director, Heart-Lung Transplant Program

Dr. Goldberg is interested in the associations between sleep-disordered breathing and cardiovascular disease. In collaboration with the Center for Sleep and the NIH-funded Clinical Translational Research Center, Dr. Goldberg is the principal investigator of an international, multi-center intervention trial for patients with central sleep apnea and heart failure. In addition, Dr. Goldberg has worked with investigators in the School of Nursing to understand the impact of sleep-disordered breathing on the behavior, quality of life and outcomes of patients with heart failure.

Nalaka Gooneratne, MD, MSCE
Assistant Professor of Medicine, Division of Geriatric Medicine

Dr. Gooneratne’s research interests are centered on studying the nature of sleep disorders in the elderly. While many older adults complain of difficulties with sleep, it is an area about which modern medicine has only a limited understanding. He has received funding through a National Institute on Aging Mentored Research Career Development Award and a National Center for Complementary and Alternative Medicine Research Award, which have supported research examining the role of melatonin, a hormone secreted by the pineal gland, in sleep in the elderly. Dr. Gooneratne also has a strong interest in the attitudes of senior citizens towards their sleep problems and how their background/ethnicity informs their decisions. Dr. Gooneratne also runs a Sleep Disorders Clinic for seniors in an effort to address the medical needs of these patients.

Indira Gurubhagavatula, MD, MPH
Assistant Professor of Medicine, Division of Sleep Medicine

Polysonomography is an expensive technology that requires that the patient has access to a sleep laboratory with trained personnel to conduct and interpret the sleep study. Dr. Gurubhagavatula’s studies explore the relative accuracies of alternative, simpler strategies for identifying cases of obstructive sleep apnea. Her research focuses on screening high risk populations in particular, such as occupational drivers who may otherwise be at risk for fall-asleep accidents. She also evaluates the relative costs of different screening strategies, and whether screening for sleep apnea can be justified on the basis of a detailed cost analysis. Dr. Gurubhagavatula also studies whether or not persons identified with sleep apnea benefit from treatment in terms of their cardiovascular risk profile. Her research has been funded by grants from the National Institutes of Health. Her clinical interests include diagnosis and management of various sleep disorders, including OSA, periodic limb movements during sleep and restless legs syndrome, narcolepsy and REM behavior disorder.
Max B. Kelz, MD, PhD
Assistant Professor of Anesthesia and Critical Care

While much research over the past decade has focused on the molecular site(s) of anesthetic action, relatively little attention has been devoted to the critical areas of the brain upon which general anesthetics exert their behavioral effects. Dr. Kelz is interested in the neuroanatomic substrates that mediate specific behavioral features of general anesthesia. New research supports an old idea that general anesthetics act in part upon the endogenous neural circuitry that governs sleep-wake cycles (the reticular activating system) to produce hypnosis. Dr. Kelz' laboratory uses behavioral and electroencephalographic analysis to identify mice with altered sensitivity to the hypnotic properties of anesthetics. By applying mouse genetics along with classic pharmacology he hopes to understand the molecular mechanisms and neural pathways leading to anesthetic-induced unconsciousness. More recently, work has begun using Drosophila as a second model organism in which to study anesthetic effects. By capitalizing upon the wealth of genetic tools available in the fly, we hope to translate basic discoveries between fly and mouse.

Kyunghee Koh, PhD
Research Assistant Professor of Neuroscience

Dr. Koh is another member of the Center for Sleep whose work is in understanding the molecular basis of circadian rhythms and sleep through her work with the fruit fly. Her research focuses on two related areas that are not currently well understood: how light entrains the circadian clock and how sleep is regulated at the molecular level. In addition to the general question of how sleep is regulated, Dr. Koh is interested in age-associated decline in sleep quality. As people get older, sleep becomes more fragmented, with frequent nighttime awakenings and increased daytime sleepiness. Results obtained from analyzing sleep/wake cycles of individual flies over their lifetime show that sleep in flies become more fragmented with age, as it does in mammals. The change occurs as a function of physiological rather than chronological age; it becomes faster or slower with manipulations of ambient temperature that decrease or increase lifespan, respectively.

Leszek Kubin, PhD
Research Professor of Physiology, Department of Animal Biology, School of Veterinary Medicine

The goals of Dr. Kubin's research are to understand the pharmacological mechanisms of REM sleep and the accompanying changes in breathing, and to identify the cellular basis of respiratory and behavioral response to sleep deprivation. To achieve these goals, the group uses a novel pharmacological model of REM sleep in rodents. To characterize the role of different neurotransmitter receptors in the regulation of sleep and breathing, in vivo pharmacology is combined with quantitative analysis of receptor mRNA and protein expression in brain regions and single cells. The rat model of chronic intermittent hypoxia provides oscillations of blood oxygen level like those in obstructive sleep apnea (OSA) patients.

Samuel T. Kuna, MD
Associate Professor of Medicine; Chief, Pulmonary, Critical Care & Sleep Section, Philadelphia VA Medical Center

Dr. Kuna's primary clinical and research interests concern the causes and treatment of sleep apnea syndrome. He is medical director of the Veterans Integrated Service Network (VISN) 4 Eastern Regional Sleep Center at the VA Medical Center, where he is also director of the Pulmonary, Critical Care and Sleep Section. He is conducting clinical research at the VA Medical Center on the ambulatory management of patients with obstructive sleep apnea and working with other members of the Center for Sleep on the heritability of sleep homeostasis. Dr. Kuna is medical director of the Centralized PSG Reading Laboratory at the Clinical Research Center for Sleep. This program standardizes the recording and analysis of sleep recordings in multicenter clinical sleep research studies. Dr. Kuna also collaborates on Dr. Michael Brennick's research on the effects of obesity on pharyngeal airway mechanics that is using innovative MRI techniques to track tissue movement in the pharyngeal walls in rodents.

Lawrence M. Levin, DMD, MD
Interim Chair and Associate Professor of Oral and Maxillofacial Surgery/Pharmacology

Dr. Levin is also Chief of the Division of Oral and Maxillofacial Surgery at the University of Pennsylvania Medical Center and Chief of the Division of Dentistry at the Children's Hospital of Philadelphia. Dr. Levin's expertise involves the use of oral appliances and orthognathic surgery in the management of obstructive
sleep apnea. Dr. Levin’s research interests include clinical trials for postoperative analgesics and the site-specific characteristics and therapeutic applications of orofacial bone marrow stromal stem cells. His clinical interests include pediatric oral and maxillofacial surgery, dental implantology, and surgical correction of dentofacial deformity.

Greg Maislin, MS, MA
Adjunct Associate Professor of Statistics in Medicine, Division of Sleep Medicine
Mr. Maislin has served as director of the biostatistics core for the Center for Sleep since 1990. He has collaborated with Dr. Pack and other center investigators for many years and has been involved in applying statistical methods to address sleep research questions since 1988. His current areas of interest in statistics include methods for randomized clinical trials, Bayesian biostatistics, propensity methods for non-randomized comparisons, and non-linear mixed models for longitudinal data. He is currently active in sleep research involving efficacy of CPAP treatment for apnea, population screening for apnea, excessive daytime sleepiness and insomnia in the elderly, differential vulnerability to partial and total sleep deprivation, and in the heritability of differential vulnerability to sleep deprivation and other sleep-related phenotypes.

Carole Marcus, MBBCh
Professor of Pediatrics; Director, Sleep Center at CHOP
Dr. Marcus’ research is focused on understanding the pathophysiology of childhood obstructive sleep apnea, and the developmental aspects of ventilatory and upper airway control. Studies have concentrated on clinical research across the age spectrum, evaluating upper airway collapsibility during sleep, as well as arousal mechanisms. In addition, in concurrent studies, she is evaluating other aspects of sleep-disordered breathing, including diagnostic techniques and treatment, with an emphasis on noninvasive ventilation.

Thornton B. Alexander Mason, MD, PhD
Assistant Professor of Neurology, Sleep Center at CHOP
Dr. Mason’s research interests include genetic influences on pediatric sleep and sleep disorders. One focus involves periodic limb movements in sleep (PLMS). Although family studies suggest a genetic basis for some cases of PLMS occurring with restless legs syndrome, no associated genes or gene products have been identified. Some data support a paucity of PLMS among normal children and a high prevalence of PLMS in children with Williams Syndrome, a human developmental disorder caused by a microdeletion of multiple genes in a distinct region of chromosome 7. Dr. Mason also acts as co-director of the Sleep Medicine Fellowship Training Program.

Lisa J. Meltzer, PhD
Assistant Professor of Clinical Psychology in Pediatrics
With an emphasis on children with chronic health conditions, Dr. Meltzer’s research interests focus on several areas related to sleep in children and their families. Her current projects include a study of the impact of disrupted sleep on mood and executive functioning in parents of ventilator-assisted children; sleep in children and parents during pediatric hospitalization; the ability of school aged children to self-report on sleep patterns, sleep problems, and sleep hygiene; the validity and utility of actigraphy in pediatric sleep research; and the diagnosis and treatment of pediatric sleep disorders in pediatric primary care centers.

Jodi A. Mindell, PhD
Associate Director, Sleep Center at CHOP
Dr. Mindell’s research focuses on the assessment and non-pharmacologic treatment of sleep problems in infants and toddlers. Dr. Mindell’s clinical interests include the treatment of pediatric sleep disorders, with a primary focus on behavioral issues of infants and toddlers; she has published several books on behavioral treatment for children with sleep problems. She is also Professor of Psychiatry and Director of the Psychology Graduate Program at St. Joseph’s University.
Adrian R. Morrison, DVM, PhD
Professor Emeritus of Animal Biology; Director, Laboratory for Study of the Brain in Sleep, School of Veterinary Medicine
Dr. Morrison has long been interested in the mechanisms underlying REM sleep. The laboratory’s investigations, together with those of the laboratory of Michel Jouvet from Lyon, France, were instrumental in the recognition of REM Sleep Behavior Disorder. The laboratory has studied this condition experimentally in cats, rats and clinically in the School of Veterinary Medicine’s hospital. The laboratory’s current focus is the role of the amygdala in the control of REM onset and its maintenance. Dr. Morrison has also been a leader in educating the public about the necessity of use of animals in biomedical research. He has recently published a book, An Odyssey with Animals: A Veterinarian’s Reflections on the Animal Rights & Welfare Debate, Oxford University Press.

Nirinjini Naidoo, PhD
Research Assistant Professor of Medicine, Division of Sleep Medicine
Dr. Naidoo’s research focuses on the molecular mechanisms of sleep regulation. She uses both the mouse and Drosophila models in her studies using biochemical and proteomic approaches to study the cellular responses to sleep deprivation. She has established that the endoplasmic reticulum is a critical sensor of perturbations that result from sleep deprivation and that a cellular protective pathway, the unfolded protein response, is induced when mice or Drosophila are sleep deprived. In addition, Dr. Naidoo is studying age-related changes in cellular protective pathways in response to sleep deprivation. Recently completed studies suggest that inadequate sleep in the elderly, who normally experience sleep disturbances, leads to an impaired cellular protective response that may in turn lead to further sleep disturbances beginning a vicious cycle of sleep loss and cellular damage. Current studies are exploring the mechanisms by which this may occur. She is also studying the role of the synaptic scaffolding protein, Homer, in sleep-wake behavior.

Cynthia M. Otto, DVM, PhD
Associate Professor of Critical Care, School of Veterinary Medicine
Dr. Otto’s research focus is on the effects of hypoxia, in particular cyclical intermittent hypoxia, on cellular responses, particularly inflammatory responses. Her laboratory has established a method to tightly control and cycle oxygen in cultured cells. The laboratory is currently investigating the effects on nitric oxide synthesis. Recent advances in the laboratory have led to novel findings in macrophages exposed to intermittent hypoxia. This line of work has been extended to evaluate the effects of intermittent hypoxia on survival in Drosophila. The main focus is the role of nitric oxide and inflammation in decreasing survival associated with exposure to intermittent hypoxia. In addition, Dr. Otto’s laboratory, in collaboration with Dr. James Baumgardner in the Department of Anesthesiology and Critical Care, is actively investigating the implications of cyclical intermittent hypoxia in acute lung injury.

Michael Perlis, PhD
Associate Professor, Department of Psychiatry
Dr. Perlis’ research interests include the etiology and pathophysiology of insomnia, health consequences of untreated insomnia, and the development of new treatments for insomnia. His clinical expertise is in the area of behavioral sleep medicine. He is the principal author of the first textbook in this field, Treating Sleep Disorders: The Principles and Practice of Behavioral Sleep Medicine. He has authored or co-authored a variety of papers and chapters on the assessment and treatment of sleep disorders and published more than 65 empirical or theoretical papers on sleep related topics.

Grace Pien, MD, MSCE
Assistant Professor of Medicine, Division of Sleep Medicine
Dr. Pien’s research interests focus on sleep disorders and women’s health. She is currently the Principal Investigator of a 5-year study of sleep and sleep-disordered breathing in midlife women from the Philadelphia area. Although it is well known that postmenopausal women are at increased risk for developing obstructive sleep apnea, the reasons are not well understood. The study examines how changes in menopausal status and reproductive hormone levels affect the development of obstructive sleep apnea in women during the menopausal transition. Her clinical interests include obstructive sleep apnea and other sleep disorders in women. She is the recipient of several prestigious academic awards, including an NIH Mentored Patient-Oriented Research Career Development Award and a Scientist Development Award from the American Heart Association.
David Raizen, MD, PhD
Assistant Professor of Neurology
Dr. Raizen joined the Center after completing a dual MD/PhD degree program followed by a neurology residency. His research is focused on two main questions: First, how are sleep and sleep-like states regulated? Second, what is the core function of sleep and sleep-like states? To address both questions, he uses the genetic model system *C. elegans*. He has established that this organism has a sleep-like state called lethargus, which occurs four times during the animal’s development. He has identified as a regulator of this state a cGMP-dependent protein kinase orPKG. The second question, the function of sleep, is approached by first identifying the changes, both anatomical and molecular, that occur during lethargus. The second step is then to ask what happens to these changes as a consequence of deprivation of sleep-like behavior.

Barbara J. Riegel, DNSc, RN
Professor of Nursing; Interim Chair, Family and Community Health Division
Heart failure remains the most common cardiac diagnosis in elders and one of the major reasons for hospital admission. Dr. Riegel provides national and international leadership in clinical research with this patient population. She is widely known for her studies of heart failure self-care and disease management and is co-editor of *The Journal of Cardiovascular Nursing*. She currently is leading a study on the impact of sleepiness on self-care in heart failure patients.

Kathy Culpepper Richards, PhD, RN
Professor of Health Promotion in Gerontology; Director, John A. Hartford Center of Geriatric Nursing Excellence
Dr. Richards is a nationally renowned sleep and geriatrics researcher. She has been particularly involved in studies about sleep patterns, disorders, and improvement through nonpharmacologic interventions (such as social activities and exercise) in older adults who have dementia. She has studied tailored biobehavioral interventions and provider practice patterns in nursing home care.

Ilene M. Rosen, MD, MSCE
Assistant Professor of Medicine; Director, Sleep Fellowship Program; Associate Program Director, Internal Medicine Residency Program, Department of Medicine
Dr. Rosen has published studies on the effects of lack of sleep on residents’ performances in *Annals of Internal Medicine* and *JAMA*. Her primary clinical interest is sleep apnea in patients with heart failure and she also treats patients with a variety of sleep disorders including circadian rhythm disorders, delayed sleep phase syndrome, idiopathic hypersomnolence, narcolepsy, restless leg syndrome, and sleep apnea.

Ann E. Rogers, PhD, RN
Associate Professor of Nursing
Dr. Rogers’ research currently focuses on the relationship of staff nurse fatigue and patient safety. Of particular interest are the effects of their work schedules, particularly extended shifts (12 hours or longer) and sleep duration. Dr. Rogers’ unique data-set includes over 22,000 days of data about the work hours, sleep patterns, errors, and drowsy driving episodes collected from 895 randomly selected full-time hospital staff nurses. She and Dr. David Dinges in Penn’s Department of Psychiatry are examining the effect of sleep duration on errors and recovery sleep obtained in a naturalistic setting. Because the majority of hospital staff nurses in the United States now work 12-hour shifts, the study is being replicated in Australia where 12-hour nursing shifts are uncommon.

Richard J. Ross, MD, PhD
Professor of Psychiatry; Staff Physician, Philadelphia VA Medical Center
Dr. Ross’ primary clinical and research interests concern the effects of psychological stress on sleep. Dr. Ross is a member of the posttraumatic stress disorder (PTSD) Clinical Team, Behavioral Health Service, Philadelphia VAMC. He treats veterans with PTSD. In his clinical research, Dr. Ross is studying the effectiveness of imagery rehearsal for the sleep and nightmare disturbance in PTSD. He has studied this form of treatment in Vietnam War veterans and is now carrying out a Department of Defense-funded investigation in veterans of Operation Iraqi Freedom and Operation Enduring Freedom. Dr. Ross does basic research in collaboration with Dr. Adrian Morrison. They are studying the effects of psychological stress on sleep in rats, including a strain otherwise known to be highly reactive to stress. Dr. Ross also collaborates with Dr. Philip Gehrman in studies of primary insomnia in humans.
Sharon Schutte-Rodin, MD
Clinical Associate Professor of Medicine, Division of Sleep Medicine
Dr. Schutte-Rodin is the Clinical Outcomes Program Director for the Sleep Medicine Division. Her clinical interests include the evaluation and treatment of all sleep disorders including sleep apnea, disorders of sleepiness such as narcolepsy, insomnia, restless legs syndrome, periodic limb movement disorder, parasomnias, and circadian rhythm disorders. In addition to practicing clinical sleep medicine, Dr. Schutte-Rodin has special interests in database development and monitoring measures of clinical effectiveness and quality improvement and clinical outcomes. A particular focus has been breathing device technology and compliance monitoring of CPAP. Recent clinical research has included apnea and reflux, apnea and glaucoma, chronic insomnia, and CPAP tracking devices. Dr. Schutte-Rodin was the American Academy of Sleep Medicine Task Force chairperson and lead author for Clinical Guideline for the Evaluation and Treatment Guidelines for Chronic Insomnia in Adults, published in the October, 2008 Journal of Clinical Sleep Medicine. She interviews for Penn medical school, does QA for the Center for Sleep, and has been a medical policy consultant for Independence Blue Cross for more than ten years.

Richard J. Schwab, MD
Professor of Medicine; Co-Director, Penn Sleep Center
Dr. Schwab’s research has focused on the pathogenesis and genetics of obstructive sleep apnea utilizing novel upper airway imaging techniques. The focus of his research is to understand the mechanisms leading to sleep apnea by evaluating the structure and function of the upper airway using physiologic imaging techniques. His studies have begun to elucidate the role of the motion of key structures of the upper airway in mediating airway closure. By examining dynamic state related changes in the upper airway and soft tissue structures surrounding the upper airway he has begun to understand the biomechanics of apneic events. He has studied patients with both magnetic resonance imaging and electronic beam computed tomography during wakefulness and sleep. Several novel findings have resulted from these studies: 1) the anatomic significance of the lateral pharyngeal walls in mediating airway caliber in normals and apneics; and 2) the characterization of the changes in upper airway caliber during the respiratory cycle and the importance of end-expiratory airway narrowing. In addition, Dr. Schwab has utilized MRI to phenotype the upper airway for genetic studies. Currently, Dr. Schwab has been investigating the relationship between obesity and sleep apnea including examining patients undergoing bariatric surgery. Finally, he has started to examine the effect of weight gain on the upper airway soft tissue structures in rats using MRI.

Amita Sehgal, PhD
John Herr Musser Professor of Neuroscience; Co-Director, Comprehensive Neuroscience Center
The goal of Dr. Sehgal’s research is to understand the molecular basis of circadian behavior, the best known example of which is the sleep/wake cycle. Dr. Sehgal’s laboratory and others have used the fruit fly, *Drosophila melanogaster*, to identify and characterize a molecular clock that drives rhythms of behavior and physiology. Mechanisms as well as molecules that comprise this molecular clock are conserved in mammals and have been implicated in at least one human circadian/sleep disorder. Efforts in the laboratory are focused on understanding the basic clock mechanism, the entrainment of the clock to environmental stimuli, such as light, and the pathways that transmit signals from the clock and produce rhythmic outputs. In addition, Dr. Sehgal’s laboratory is using the fly model to understand the function of sleep, as well as the control of sleep by non-circadian mechanisms, i.e., by the homeostatic mechanisms that drive the need to sleep independently of the circadian clock.

David Stanton, MD, DMD
Associate Professor of Oral Surgery and Pharmacology, School of Dental Medicine
Dr. Stanton is a graduate of both the University of Pennsylvania School of Medicine and the School of Dental Medicine. He is the program director of the Oral and Maxillofacial Surgery residency program and course director of the third-year oral surgery course at Penn Dental Medicine. He has lectured nationally on several of his fields of interest, including cosmetic facial surgery, obstructive sleep apnea, and maxillofacial trauma. His research interests include OSA, hair transplantation and facial trauma. He is currently a member of the examination committee of the American Board of Oral and Maxillofacial Surgery. He is also a section editor for the Oral & Maxillofacial Surgery Self Assessment Tool (OMSSAT), the national in-service training examination for Oral & Maxillofacial Surgery residency programs.
Steven A. Thomas, MD, PhD
Associate Professor of Pharmacology
One goal of Dr. Thomas’ lab is to define the systems that contribute to specific behaviors, and to understand the mechanisms that underlie these behaviors. Such knowledge will ultimately permit the prevention and treatment of mental illness. Recent advances in transgenic technology allow the analysis of specific genetic alterations in the context of the whole organism. The lab is pursuing several fundamental observations including the critical role of norepinephrine in synaptic plasticity, learning and memory, sleep/wake regulation, anxiety, aggression, maternal behavior and the mechanisms of antidepressant drug action.

Nancy C. Tkacs, PhD, RN
Associate Professor of Nursing
Dr. Tkacs’ research is based in the study of the pathophysiological adaptation to a variety of disease-induced stressors. Her present focus is characterizing neurobiological changes in a rodent model of hypoglycemia unawareness. This disabling condition limits the use of intensive management in patients with type 1 diabetes, resulting in psychological as well as physical morbidity. Having successfully characterized suppressed hormone responses to recurrent hypoglycemia in rats, Dr. Tkacs is studying brain alterations associated with this model as one way to develop targeted interventions to treat this condition.

Sigrid Veasey, MD
Associate Professor of Medicine, Division of Sleep Medicine
Dr. Veasey’s laboratory focuses on neural injury incurred by hypoxia/reoxygenation events of obstructive sleep apnea. Over the past year her lab identified the specific wake-active neuronal populations injured by hypoxia/reoxygenation and the two catecholaminergic groups – the noradrenergic locus coeruleus and dopaminergic periaqueductal grey wake neurons. By comparing phenotypes and responses in these vulnerable to resistant wake neuronal populations, her group identified NADPH oxidase as a major contributor to the oxidative injury. Dr. Veasey is now comparing and contrasting these responses with other groups of neurons known to be injured in obstructive sleep apnea. The goal is to find major mechanisms of injury in hippocampal, hypothalamic and cortical neurons and then begin translational studies to identify the optimal overall pharmacotherapeutic approach to prevent or minimize neural injury in sleep apnea.

Terri Weaver, PhD, RN
Ellen and Robert Kapito Professor of Nursing Science; Chair, Biobehavioral and Health Sciences Division, School of Nursing
Dr. Weaver’s interdisciplinary research focuses on characterizing outcomes associated with sleep disorders and their treatment, particularly treatment adherence. She developed the first instrument to measure functional status in disorders of excessive sleepiness. She recently completed a study designed to isolate factors contributing to non-adherence during the first week of treatment. She is the principal investigator of an international multi-center randomized placebo-controlled clinical trial study designed to evaluate the efficacy of CPAP treatment for milder OSA on functional status, daytime sleepiness, and blood pressure.
Original Articles


Naidoo, N. Sleep deprivation, aging and cellular stress. Frontiers in Neuroscience, Sleep and Dreams. 2009 December; 3(3):


Books/Chapters


Allan Pack, MBChB, PhD, is the principal investigator on an R01 grant entitled "A family linkage study of obstructive sleep apnea" with colleagues in Iceland to determine genes that confer risk for sleep apnea. He also holds a five-year grant from the National Institute of Aging at the NIH to study the mechanisms of alterations in sleep with age. Dr. Pack also oversees two training grants: one to train postdoctoral and predoctoral students in both nursing and neuroscience in the area of sleep and sleep disorders, and the second to train physician-scientists in the area of respiratory neurobiology and sleep. In addition, with other investigators in Penn's School of Medicine, he holds a K12 from the NIH for career development in genomic/genetic studies in lung diseases and sleep disorders. This year, Dr. Pack, with other investigators in the Center for Sleep, received funding for a program project from the National Heart, Lung and Blood Institute (NHLBI) on endophenotypes of sleep apnea and role of obesity. Penn's Institute on Aging, Dr. Abel is a collaborator on the project "Interactions of protein aggregation in Parkinson's dementia" that examines behavioral changes in mouse models of Parkinson's disease. He also oversees a training grant in behavioral/cognitive neuroscience.

Michael Brennick, PhD, is the principal investigator on an R01 entitled "Obesity effects on pharyngeal airway mechanics by MRI" designed to determine the effects of obesity of pharyngeal airway mechanics in a Zucker rat model. He is also a co-investigator on Dr. Pack's grant "Endophenotypes of sleep apnea and role of obesity" on the project "Understanding the relationship between obesity and tongue fat in humans and rats," with a specific focus to determine the effect of weight gain on abdominal visceral fat (measured by MRI), tongue fat (measured by MRI and biochemically), tongue volume, and airway size in two rat models of obesity.

Ted Abel, PhD, has an R01 from the National Institute for Mental Health to study the molecular basis of long-term memory storage which is currently in its second five-year funding period. He is also the co-investigator – with investigators from George Mason University and Glasgow University - on a Collaborative Research in Computational Neuroscience grant, "Spatial and temporal aspects of cAMP/PKA signaling underlying information processing." Dr. Abel is the principal investigator of another collaborative program grant with investigators from the United Kingdom, Italy and the USA. This Human Frontier Science Program uses genetic, proteomic, computational and cell biological approaches to study the role of PKA anchoring in synaptic plasticity.

He is a collaborator with Dr. Pack in studying the mechanisms of alterations in sleep with age, and with

Dr. Norma Cuellar is the principal investigator on a grant studying the effects of valerian on sleep in persons with restless legs syndrome. She has two other grants in review, one building on the valerian study in patients with RLS and the other examining the effects of mindfulness meditation on sleep in postwar Iraqi and Afghanistan veterans with PTSD.

Dr. David Dingess holds several grants including those from the NIH and NASA as well as other sources of funding. The National Institute of Nursing Research supports his study "Neurobehavioral effects of partial sleep deprivation," which focuses on the systematic assessment of recovery from chronic sleep restriction by determining the effects of recovery of two successive sleep periods of different durations. The National Aeronautics and Space Administration supports his work for the National Space Biomedical Research Institute testing optical computer recognition of stress, affect, and fatigue during performance in space flight.

Philip Gehrman, PhD, currently receives funding from the NIH to study stress reactivity in insomnia and from the Department of Defense for cognitive behavioral treatment for nightmares in Operations Iraqi Freedom and Enduring Freedom (OIF/OEF) veterans.

Dr. Nalaka Gooneratne currently has an NIH grant to study sleep disorders and quality of life in elderly lung cancer survivors and another grant to examine the long-term consequences of insomnia in older adults.

Indira Gurubhagavatula, MD, MPH, has funding from the Centers for Disease Control National Institute for Occupational Health and Safety to evaluate how well self-assembled technologies used in the home setting identify sleep apnea in commercial drivers and determine whether occupational screening can be combined to reduce the number of patients that need testing. She is also a co-investigator on a grant from NHLBI on the inflammatory response to sleep apnea in obese subjects, the primary aim of which is to test whether CPAP therapy induces inflammation as determined by serum highly-sensitive C-reactive protein concentration, more than weight loss alone, and whether combining weight loss and CPAP therapy yields a greater reduction in inflammation than either alone.

Dr. Max Kelz is the principal investigator on grants from the NIH including one entitled, "Arousal, orexins and anesthesia," the goal of which is to investigate the consequences of genetic and pharmacologic...
manipulation of the hypocretin/orexin system upon the hypnotic properties of volatile anesthetics as determined by behavioral as well as EEG analysis. He also holds a grant from Penn’s Institute for Translational Medicine and Therapeutics for “Neural inertia: an obstacle to cognitive return, a new view of arousal state control,” to uncover genetic determinant of volatile anesthetic induction and emergence in flies and mice; and a grant from the Comprehensive Neuroscience Center at Penn on “Severe sleepiness and the lateral hypothalamicus” to discover a theoretical yet currently undiscovered population of wake-active neurons in the lateral hypothalamus.

**Dr. Leszek Kubin** holds several grants from the NHLBI including “Premotor control of upper airway and REM sleep atonia;” “Episodic hypoxia, hypothalamic and insulin resistance;” “Hypothalamo-brainstem control of sleepiness and arousal;” and “A rodent model of compromised upper airway.”

**Samuel Kuna, MD,** is the University of Pennsylvania clinical site PI for the Sleep AHEAD study (Action for Health in Diabetes), a multicenter study to determine the effect of weight loss on obstructive sleep apnea, directing the centralized polysomnogram reading laboratory for the study. He is also the PI on a Veterans Health Administration grant to examine cost-effective strategies to evaluate veterans with sleep apnea. He is a co-investigator on a grant from NHLBI to determine the effects of obesity of pharyngeal airway mechanics in a Zucker rat model and on an NIH GO grant titled “Developing interactive technologies to improve research and health behavior.” Dr. Kuna also acts as a project leader on “Responses to CPAP treatment in obese and lean sleep apnea patients,” the overall goal of which is to determine the effect of obesity on the response to CPAP treatment in patients with OSA.

Director of the Sleep Center at CHOP, **Dr. Carole Marcus** holds several grants. She is the principal investigator on a grant from the NHLBI on the pathophysiology of childhood OSA. She also holds a grant from Phillips Respironics to determine the effect of different types of positive airway pressure treatments on adherence and efficacy in children with OSA. She is co-investigator on several studies including a randomized controlled study of adenotonsillectomy for childhood sleep apnea supported by the National Center on Sleep Disorders Research, an R01 to study the mechanism of oxyhemoglobin desaturation and vasculopathy in children with sickle cell disease, another R01 on mechanisms of sleep-disordered breathing in the menopausal transition. A grant from the University of Pennsylvania’s University Research Foundation on interdisciplinary approaches to the treatment of OSA in obese adolescents is pending.

**Adrian Morrison, DVM, PhD,** holds a grant from the NIH on amygdalar modulation of fear-conditioned changes in REM sleep.

**Nirinjini Naidoo, PhD,** has an American Recovery and Reinvestment Act (ARRA) Challenge Grant entitled “Biomarker for sleep loss: a proteomic determination” which will explore changes in blood proteins that occur with sleep loss and determine whether there are differences between subjects who are resistant to the effects of sleep deprivation and those who show a marked behavioral response. She also is a collaborator on a Center pilot grant with Dr. Joseph Baur, an endocrinologist, to study the relationship between sleep loss, glucose metabolism and the ER stress response.

Associate Professor of Psychiatry **Michael Perlis** is a co-investigator on two R01s to study insomnia. In one, they further explore the critical components of attentional processing with a view to identifying a candidate ‘marker’ for insomnia. This research may help define what insomnia is (beyond the subjective experience of the disorder) and how and why it confers risk for other illnesses. Another grant investigates the ‘placebo effect’ and hopes to advance from a descriptive to an experimental analysis of the placebo effect, and examine the clinical implications of partial reinforcement as it is applied to the treatment of insomnia. The value of this proposed research is in its capacity to provide for the long-term treatment of insomnia in a manner that increases the durability of pharmacotherapy while reducing the overall amount of medication required.

**Grace Pien, MD,** is the principal investigator on an R01 “Mechanisms of sleep-disordered breathing in the menopausal transition,” publishing some of her findings this year in the journal Sleep.

**David Raizen, MD, PhD,** holds an R01 entitled “The regulation of sleep-like behavior in C. elegans” which funds research aimed at understanding the genetic and cellular regulation of lethargus in these worms. He also received the McCabe pilot grant from the University of Pennsylvania, designed to support promising research, to further his study of the transcriptional signature of a sleep-like state in C. elegans.

**Professor Kathy Richards** is the principal investigator on an R01 from the NIH that aims to validate measures of restless leg syndrome in elders with memory disorders. She is co-investigator on several other grants held by Nursing Science faculty including a study of individualized care for at-risk older adults and interventions to improve CPAP adherence.

**Dr. Barbara Riegel** holds several grants from the NIH studying heart failure self-care in the elderly. She is the principal investigator on an R01 that explores the impact of sleepiness on self-care of heart failure patients. She is PI on another grant that looks at outcomes in promoting self-care using tele-homecare. She is co-investigator on an additional grant that looks at heart failure self-care and one on disparity in cancer pain outcomes.

**Associate Professor of Nursing** **Ann Rogers** is principal investigator on an NIH-funded grant, the goal of which is to extend sleep in obese patients to promote weight loss.

**Richard Schwab, MD,** is the PI on an R01 from the NHLBI title “Obesity and OSA: understanding the importance of tongue fat and metabolic function” that compares the tissue properties and metabolic function of the tongue and other upper airway soft tissue structures in apneics and weight-matched controls without apnea; and contrasts the changes in tissue properties and metabolic function of the tongue and other upper airway changes in soft tissue structures in apneics and weight-matched controls with similar degrees of weight loss. He is also a collaborator on Dr. Pack’s “Family linkage of study of sleep apnea,” Dr. Pien’s “Mechanisms of sleep-disordered
breathing in the menopausal transition, “Dr. Brennick’s “Obesity effects on pharyngeal airway mechanics by MRI,” and the Sleep AHEAD Study. He also is a project leader in the Program Project Grant, “Endophenotypes of sleep apnea and role of obesity,” specifically studying “The relationship between obesity and tongue fat in humans and rats.”

Amita Sehgal, PhD, holds a Howard Hughes Investigator award through 2012. She is also the principal investigator on a grant from the NIH to study the cycling of circadian rhythm proteins. She is the co-investigator, with Dr. Pack, on the mechanisms of alterations in sleep with age. Members of Dr. Sehgal’s laboratory have funding to study the neurochemical regulation of sleep, characterization of a novel gene required for sleep in Drosophila, identification and characterization of kinases and phosphatases involved in light entrainment of the Drosophila clock, and the function of sleep in the regulation of stem cell activity.

Nancy Tkacs, PhD, RN, an associate professor in the School of Nursing, holds a grant from the NIH to study the role of corticosterone on hippocampal cell proliferation in mice with diabetes. She also has funding from the Juvenile Diabetes Research Foundation to study juvenile hypoglycemia and loss of hypoglycemic arousal and from the School of Nursing Educational Initiatives/Investing in the Future on the “Advanced physiology and pathophysiology technical initiative proposal.”

Dr. Sigrid Veasey currently holds two R01s, one entitled “Intermittent hypoxia: mechanisms of hypsomnolence.” This award is used to identify the groups of wake-active neurons susceptible to sleep apnea oxygenation conditions and then to examine how the injury occurs. To date, we have discovered that the catecholaminergic groups are most affected and that NADPH oxidase contributes to the selective oxidative injury and that there is endoplasmic stress injury as well. The other R01, “Sleep apnea: upper airway nerve injury,” is designed to identify the mechanisms of sleep apnea oxygenation injury on upper airway motoneurons. We have found a significant stress injury in the endoplasmic reticulum (ER) in selective motoneurons; spinal, hypoglossal and facial more so than trigeminal and ocularmotor. We also found the injury can be prevented by dietary modification: lower advanced glycation end products by cooking foods at lower temperatures. The ER stress pathway identified is the p-PERK pathway and by increasing phosphorylation of eIF-2a we may also lessen injury. This work is poised for clinical translation to determine whether humans with sleep apnea have the same injury and if so, can we prevent it.

Terri Weaver, PhD, RN, is currently a co-investigator on an R01 on the impact of sleepiness on heart failure self-care, which aims to describe the transient, reversible factors associated with excessive daytime sleepiness (EDS) in persons with heart failure. She is also co-investigator on a grant to look at risk assessment and tailored intervention to improve CPAP adherence.
THE PENN SLEEP CENTER
2009 ANNUAL REPORT
WAS PRODUCED BY
Margaret Stone Higgins

A SPECIAL THANKS TO
THE FOLLOWING FOR
THEIR CONTRIBUTIONS:

Design and Printing
Penn Publication Services

Photography
Dan Burke