

Neurobiology of Sleep and Waking

WORKSHOP REPORT

Sponsors:

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Neuroscience Center

Bethesda, MD

Co-Chairs:

David F. Dinges, Ph.D.

Thomas Roth, Ph.D.

Participants:

Ravi Allada, M.D.

Mary A. Carskadon, Ph.D.

Robert Greene, M.D., Ph.D.

Husseini K. Manji, M.D.

Emmanuel Mignot, M.D., Ph.D.

Eric Nofzinger, M.D.

Gary S. Richardson, M.D.

Clifford B. Saper, M.D., Ph.D.

Ronald S. Szymusiak, Ph.D.

Fred W. Turek, Ph.D.

Daniel J. Buysse, M.D.

Pierluigi Gambetti, M.D.

Steve Henriksen, Ph.D.

Una McCann, M.D.

Robert Y. Moore, M.D., Ph.D.

Allan I. Pack, M.D., Ph.D.

Larry D. Sanford, Ph.D.

Jerome Siegel, Ph.D.

Guilio Tononi, M.D., Ph.D.

“My creativity diminishes, my irritability increases, my disposition suffers, my outlook is gloomier, my muscles feel weaker, my energy is kaput some days. Some days I’m too tired to accomplish anything but still unable to nap or sleep. It’s an odd sensation. I feel as if I’ve been deprived of sleep and am exhausted but at the same time, as if I had drunk 5 cups of coffee and were overstimulated.”

-Patient with insomnia (courtesy of Dr. Dan Buysse)

Insomnia is a symptom of difficulty initiating sleep, maintaining sleep, or non-restorative sleep associated with some type of daytime consequence. Insomnia is both a disorder (i.e. primary insomnia) as well as occurring secondary to medical, psychiatric, sleep or circadian rhythms. Daytime sequelae include altered mood, impaired functionality, increased absenteeism and an increased risk for depression. The prevalence of chronic insomnia is estimated to be about 10% of the adult American population with an additional 25% of the population experiencing occasional sleep difficulty.

The purpose of the workshop was to enhance understanding of insomnia, to consider research gaps and opportunities, and to develop a report with recommendations. Despite a prevalence of 10% in the U.S. population and 20–25% in primary care settings, insomnia has received little basic scientific inquiry. A fundamental barrier to advances in basic science on the mechanisms of insomnia continues to be the lack of a clearly defined phenotype(s) based in objective findings. For example, objective differences exist between insomniacs and naturally short sleepers. More importantly, the consequences of insomnia are qualitatively different from those of sleep deprivation. While sleep deprived individuals show sleepiness during the day, patients with insomnia show increased alertness. Taxonomies for codifying insomnias and treatments for insomnia have been developed from clinical descriptions, making it difficult to develop animal models that contain the phenotypic characteristics of certain insomnias. Various physiological parameters (signs) have been suggested to characterize insomnia (see appendix), but these are not universally accepted or used. There may be many pathophysiologies to insomnia, and it remains unknown whether so-called “primary insomnia” is a homogeneous disorder, or whether it is distinct from or on a continuum with insomnia associated with major affective disorders. The situation is further complicated by indications that the nature of the sleep symptom in a given patient are not stable, changing over time in 50% of patients. Nevertheless, half of severe cases of insomnia tend to remain severe after a period of 4 months. There is a dearth of neurobehavioral and neurobiological evidence on whether transient insomnia and chronic insomnia have fundamentally different pathophysiologies.

Insomnia increases with age; it is twice as common in women than men; and there is substantial comorbidity between insomnia and depression. These risk factors suggest that fundamentally different neurobiological mechanisms may underlie diagnostic entities of insomnia. It is widely believed that *chronic insomnia* results from predisposing factors, precipitating factors, and perpetuating factors, suggesting that its etiology is viewed clinically as multifactorial and complex (see appendix). However, the basic mechanisms by which these hypothesized components occur or function remain unknown. There is clinical research evidence that chronic hyperarousal contributes to insomnia, but the biological basis for this hypothetical construct and the mechanism by which it alters sleep action on sleep remain unstudied. A growing number of clinical studies suggest that pharmacotherapies and cognitive behavior therapies can successfully treat insomnia. There are indications that the failure to obtain effective treatment for chronic insomnia can lead to behavioral disability, including impairment of social roles, alcohol abuse, and predisposition to depression. The processes by which efficacious treatments of insomnia alter the basic neurobiology of sleep and waking may also provide opportunities for advances in basic science on the causes and consequences of insomnia.

In short, the conceptual models of insomnia have not yet been adequately back translated to neurobiology. However, as the following list reveals, growing knowledge and techniques in the neurobiological regulation of sleep homeostasis, circadian rhythms, stress and arousal, conditioning, and emotion and cognition, offer new opportunities to investigate insomnia in novel and fundamental ways. The following research questions were raised at the workshop.

1. A central problem in the study of insomnia is the absence of a phenotypic marker for the spontaneous disruption of sleep in combination with its subsequent state of alertness experienced by many insomniacs. This limits (1) generalizability across human studies; (2) the development of animal models of the disorder; and (3) the use of genetic approaches. Insomnia phenotypes must be developed to accelerate advances into the basic mechanisms of insomnia. Since the incidence of insomnia is higher among women than men, and higher in older adults than in younger adults, there is a need to ensure that phenotypes reflect these vulnerable populations. Establishing phenotypes for insomnia would also help in the

search for biological and behavioral risk factors for the development of insomnia across the life span, and would lead to genetic studies of families in which phenotypic markers aggregate. In addition, there is a need to develop animal models of insomnia (e.g., using fear-conditioning, mutagenesis, model systems) where basic mechanisms can be identified. For example, there is evidence of similarities between rest in *Drosophila* and sleep in mammalian species, suggesting opportunities for novel phenotyping of key behavioral features of insomnia that could lead to discovery of basic mechanisms of insomnia.

2. Daytime complaints (involving mood, concentration, etc.) are common in persons with insomnia, which requires that the disorder be understood as one of waking neurobehavioral functions as well as sleep. It remains unclear, however, how the chronic loss of sleep at the levels apparently experienced by many patients with insomnia can result in waking neurobehavioral deficits. While cumulative cognitive deficits from chronic sleep reductions have been experimentally demonstrated in healthy adults, such studies have not been undertaken in patients with insomnia. An alternative possibility to the hypothesis that sleep debt results in waking deficits in insomnia, is the hypothesis that other factors, such as hyperarousal during sleep, extend into wakefulness, disrupting aspects of waking function as well as sleep. It is also possible that insomnia can derive from disruptions of waking neurobiology (e.g., affect regulation, stress reactivity, arousal) that extend into sleep. These somewhat contradictory theoretical explanations highlight the need for in-depth studies of both sleep and waking neurobehavioral and neurobiological functions in insomnia.
3. Physiologic hyperarousal (e.g., elevated metabolic rate; sympathetic nervous system activity) is considered to be characteristic of primary insomnia. Despite complaints of inadequate sleep, insomniacs show significantly reduced sleep propensity during the daytime on the multiple sleep latency test (MSLT) than do non-insomniacs. It remains unknown whether these signs of hyperarousal are etiologic or symptomatic. Studies are needed to determine whether primary insomnia is fundamentally a disorder of stress regulatory mechanisms. Given the potentially critical role of corticotrophin releasing hormone (CRH) and its regulation of the hypothalamic pituitary adrenal axis and central noradrenergic systems, new techniques are needed to measure CRH activity in the diagnosis and follow up of patients with primary insomnia. Similarly, some attention should be given to the possibility of treating primary insomnia with specific CRH antagonists. Chronic primary insomnia is also associated with an elevated risk for major depressive and anxiety disorders. More research is needed on the natural history of primary insomnia, as well as on the effectiveness of long-term pharmacotherapy for insomnia in preventing development of mood disorders.
4. The role of developmental factors in precipitating insomnia during early development, childhood, adolescence and young adulthood has received scant attention. Research is needed on the changes in brain development, hormonal, and metabolic factors that may contribute to insomnia with and without affective disorders in these age groups.
5. Insomnia prevalence is higher in older adults than in younger adults, but the mechanisms contributing to its increasing incidence with advancing age remain unknown. At the cellular and molecular level, it has been shown that there are age-associated changes in afferent and efferent pathways of the suprachiasmatic nucleus (SCN), the biological clock that controls the circadian patterning of many neural, endocrine, and behavioral functions. It is quite possible that disruption in the integrative neural systems could have serious deleterious effects in the function of other organ systems. It has not been resolved whether decreased or displaced secretory profiles for circadian-mediated (e.g., melatonin) and/or

sleep-mediated (e.g., growth hormone) endocrine functions contribute to the increased prevalence of insomnia in the elderly. There is a need to establish the effectiveness for treating insomnia as well as the basic mechanisms involved in effective treatment via pharmacotherapies based in neuroendocrine functions (e.g., OTC melatonin; estradiol with or without progesterone for post-menopausal women; drugs that promote growth hormone production). The elucidation of these and related hormonal and neurotransmitter (e.g., adenosine) mechanisms, may lead to the development of more effective and targeted pharmacological approaches to alleviate some of the problems of sleep that afflict over half of the older population.

6. Functional genomics and proteomics offer important new strategies for investigating insomnia. Studies of gene and protein expressions involved in sleep, waking and the transitions between the two states may be particularly relevant to insomnia. Transcription studies might help identify relevant genes in insomnia. Individual differences in sensitivities in gene expression might also prove a fruitful avenue for research.
7. Studies of gene expression in short and long-term sleep deprivation in rats suggest that noradrenergic activity is critical to the genes activated during waking and sleep deprivation. Research is needed on the role of noradrenergic mechanisms in the induction and maintenance of wake during sleep. Chronic total sleep deprivation in rats appears to activate the gene for a protein that catabolizes amines at the mitochondrial level. This suggests that when sleep is chronically inadequate, the brain may be exposed to uninterrupted firing of monoaminergic systems, which results in a compensatory increase of enzymes to metabolize the elevated amines. Basic studies are needed to determine whether the molecular consequences of chronic insomnia are similar to those of long term sleep deprivation. It is also unknown whether chronic insomnia is associated with chronic activation of the catecholaminergic system.
8. Adenosine functions in the central nervous system to impede neuronal firing, and adenosine receptors in the basal forebrain have an inhibitory tone on cholinergic neurons, which when not inhibited contribute to thalamocortical activation. There is evidence that adenosine receptor 1 knockout mice show no response to adenosine, resulting in less sleep (i.e., a putative animal model of insomnia). Following sleep deprivation, these knockouts have more sleep, but not more EEG slow wave activity, suggesting that the A1 receptor has a role in facilitating wake to sleep transition and slow wave sleep (the putative marker of homeostatic sleep drive). More research is needed to determine whether alterations in adenosine receptors could account for the elevated fatigue and presumed reduced recovery potential of sleep in insomnia.
9. The preoptic anterior (POA) hypothalamus may have a key role in certain insomnias. Subsets of POA neurons are involved in arousal, while others become activated during sleep. Lesions in hypothalamic POA area cause insomnia, while injections of somnogenic agents in this region promote sleep. What are the molecular, cellular and electrophysiological mechanisms by which POA neuronal subsets for sleep and waking are differentially activated and suppressed? How might these mechanisms shed light on a possible pathway for insomnia and how might they be harnessed to yield promising new pharmacotherapies for insomnia?
10. Lesions of the ventral midbrain produce phasic muscle tone, insomnia, and REM-sleep behavior disorders. Since the pathology of Parkinson's disease is in the ventral midbrain, it would be important to determine whether there is a progression from insomnia to

Parkinson's disease. The ventral midbrain may also have a role in stress-related sleep disorders, such as PTSD. More studies are needed on how alterations in the ventral midbrain contribute to sleep disruption.

11. Hypocretin/orexin, an excitatory peptide with two receptors located in lateral hypothalamic neurons that project widely rostrally and dorsally, has been found to be deficient in narcolepsy, but not insomnia. Increased hypocretin activity has been observed during waking and at the end of sleep. More electrophysiological and high-resolution dialysis studies are needed on the mediation of hypocretin cells by both monoaminergic and non-monoaminergic activity, and in general on how an intact hypocretin system may play a role in difficulty falling asleep or maintaining sleep.
12. The ventrolateral preoptic (VLPO) area contains galaninergic and GABA-ergic cells that promote sleep. VLPO neurons increase their firing rates during sleep, while lesions in the VLPO area can lead to sustained wakefulness in animals. VLPO neurons get inputs from retina, cortex, and brainstem. Studies of how VLPO-mediated sleep maintenance can be disrupted via input from these pathways may yield insights into basic mechanisms of arousal during NREM and REM sleep. Evidence that the galaninergic cell group in the VLPO shrinks with age in humans raises the possibility that this cell group may be the basis for insomnia that develops in the elderly. Research is needed on the extent to which VLPO degeneration contributes to age-related insomnia.
13. In addition to narcolepsy-like symptoms, insomnia was recognized to be one of the consequences of encephalitis lethargica. Histaminergically mediated neurons in the tuberomammillary nucleus (TMN) were discovered to be involved, suggesting that studies of TMN function may be another avenue for neurobiological discoveries relevant to insomnia.
14. Given the precipitation and apparent maintenance of insomnia by emotional distress, the relationships between the neurobiology of emotion and the neurobiology of sleep regulation is a potentially fruitful avenue for discovery. There is animal evidence that conditioned fear stimuli associated with an aversive situation can affect sleep as much as the aversive stimulus itself, and that genetic background influences vulnerability to such conditioning. The amygdala, which is critical for conditioned fear has connections to monoaminergic nuclei involved in waking arousal, and it modulates responsivity to environmental stimuli (i.e., alerting). Hence the amygdala plays a global role in regulating arousal and response to stimuli. There is a need to determine whether the amygdala could trigger alerting responses during sleep. The amygdala could also play a role in insomnias associated with affective disorders and conditioned insomnias.
15. Fatal familial insomnia (FFI) and its sporadic form (sFI) are two phenotypically similar prion diseases characterized by the loss of the ability to sleep (especially nonREM sleep) and other related circadian rhythms, dysautonomia and motor signs associated with early and severe neuronal loss in thalamic nuclei, especially of the medial dorsal and anterior ventral nuclei. Although the pathogenic mechanism remains to be identified, evidence suggests that the D178N- 129M mutated PrP likely plays a central role in the sleep impairment of FFI and sFI, pointing to normal PrP as having a role in sleep regulation. It has been proposed that the severe neuronal loss in medial dorsal and anterior ventral thalamic nuclei disconnects the limbic cortex from the brain stem, leading to a generalized activation syndrome (GAS) with inability to sleep, autonomic and motor activation. This hypothesis is supported by the observation that Morvan's chorea, a rare autoimmune disorder, and delirium tremens are also characterized by the inability of generate slow wave sleep, and by autonomic and motor

over activation, and both are related to thalamic dysfunction. However, in FFI and sFI the presence of the mutated PrP and PrP^{Sc} in the brain of FFI and sFI patients is widespread and goes far beyond the thalamus. Therefore, other mechanism and brain locales cannot be excluded. Animal models may serve to clarify the mechanisms of sleep impairment in FFI and sFI.

16. The well replicated clinical effects of sleep deprivation as an anti-depressant stand in stark contrast to the absence of scientific studies on mechanisms by which sleep loss can evoke mania in patients with bipolar disorder, and the nearly complete insomnia that accompanies it. There is also an acute need for experiments that precisely characterize biological markers of sleep homeostasis, circadian rhythmicity, and waking neurobehavioral functions when sleep deprivation is used as an anti-depressant in bipolar disorder.
17. Neuroimaging and quantitative EEG studies suggest that the ventro-medial prefrontal cortex (PFC) may be central to the regulation of sleep, affect and cognition. Dysfunction in this area has been hypothesized to be associated with NREM sleep and to underlie the perseverative thoughts and behaviors of many insomniacs. Similarly, the medial PFC is activated in REM sleep, and anterior paralimbic structures have been hypothesized to subservise insomnias associated with REM dysfunction. More research is needed on these hypotheses and the mechanisms underlying signs and symptoms of insomnia.
18. Studies of corticotrophin releasing hormone (CRH) and its effects on the hypothalamic pituitary axis, the sympathetic nervous system, and GABA receptors in the brain may shed light on the mechanisms by which emotional disturbance and insomnia can co-occur. Animal models such as maternal separation may shed light on vulnerability to depression and insomnia. Variations in genetic backgrounds could be explored to determine whether insomnia, anxiety and depression share the same or different genotypes.
19. There is a need to determine what roles abnormal circadian physiology and/or volitional changes in sleep-wake behavior play in the initiation and maintenance of delayed and advance sleep phase syndromes (DSPPS and ASPS). What are the mechanisms by which the sleep-wake cycle becomes displaced in circadian time in DSPPS or ASPS, and resistant to re-entrainment to a desired circadian phase? What are the neurobiological mechanisms by which the circadian system could contribute to a wake-up signal at sleep onset or during sleep?
20. The role of drug use and abuse in predisposition toward, precipitation of, and perpetuation of insomnia remains poorly understood. Research is needed in this area, especially pertaining to alcohol and related recreational drug use (e.g., MDMA, GHB) in adolescents and young adults. Studies are also needed on the pharmacology of these recreational drugs relative to sleep initiating and sleep maintenance neurobiology.
21. Insomnia and objectively disturbed sleep are prominent clinical features in abstinence syndromes for alcohol and other drugs of abuse. There may be important overlap between basic mechanisms involved in these syndromes and those involved in primary insomnia. It remains unclear to what extent this overlap may underlie the epidemiological link between insomnia and substance abuse. Similarly, it is not known what role sleep disturbance may play in recidivism during abstinence.

APPENDIX

Definition of insomnia as a clinical syndrome:

- Symptom of difficulty falling or staying asleep, or non-refreshing sleep.
- Adequate opportunity for sleep.
- Waking consequences:
 - affective (irritability, variability).
 - cognitive (concentration, attention, memory).
 - altered quality of alertness (fatigue with inability to sleep).

Signs of insomnia:

- Polysomnographic measures
- Quantitative EEG
- CNS imaging feature
- Hormonal measures
- Daytime alertness (MSLT)
- SNS activity

Conceptual model for the development of insomnia (Spielman & Glovinsky; Buysse):

- Predisposing factors
 - genetic, individual differences
 - anatomic or functional lesions in specific neurotransmitter systems
 - hyperarousal
- Precipitating factors
 - developmental events (e.g., adolescence, aging)
 - fear conditioning
 - disease
 - environmental circadian challenge
- Perpetuating factors
 - contextual conditioning
 - behavior

WORKSHOP AGENDA

CO-CHAIRS

David F. Dinges, Ph.D.

Thomas Roth, Ph.D.

MONDAY, SEPTEMBER 10, 2001

OPENING SESSION

Moderator: Thomas Roth, Ph.D.

- 8:30 Carl E. Hunt, M.D. Welcome and Orientation
- *Purpose and goals of Workshop*
- 8:40 David F. Dinges, Ph.D. The Need to Identify Basic Mechanisms of Insomnia
- *Overview of insomnia: descriptive paradigms, basic science paradigms, variable manifestations*

SESSION 1: NEUROBIOLOGY OF SLEEP GENERATION, MAINTENANCE AND AROUSAL

Moderator: Fred W. Turek, Ph.D.

- 9:00 Ronald S. Szymusiak, Ph.D. Hypothalamic Mechanisms of Sleep Generation
- *Review the role of the preoptic/anterior hypothalamus in the generation of sleep via its inhibitory descending control of arousal-related monoaminergic cell groups. Discuss aspects of basal forebrain neurobiology that could be involved in the various manifestations of insomnia.*
- 9:30 Emmanuel Mignot, M.D., Ph.D. Hypocretin System Modulation of Sleep and Arousal
- *Review the evidence for hypocretins as major sleep-modulating neurotransmitters. Discuss aspects of the hypocretin system that may be relevant to the various manifestations of insomnia.*
- 10:00 David Weaver, Ph.D. Molecular-Cellular Biology of the Circadian Clock and Melatonin Receptors
- *Review the genes and proteins involved in the transcriptional-translational feedback loop of the mammalian cell-autonomous circadian clock. Review the evidence for melatonin receptors in the SCN and other brain areas. Discuss how circadian clock proteins and melatonin receptors may be relevant to the various manifestations of insomnia.*
- 10:30 Break

10:50 Robert Y. Moore, MD, Ph.D. SCN Functional Anatomy in Sleep and Waking

- *Review the evidence for the SCN's role in arousal via its connections to the posterior hypothalamic area. Describe the source of afferent connections to the posterior hypothalamic area. Discuss aspects of SCN-PHA neurobiology that may be relevant to the various manifestations of insomnia.*

11:20 Panel Session Speakers
Open Discussion

12:15 *Lunch*

SESSION 2: NEUROBIOLOGY OF SLEEP GENERATION, MAINTENANCE AND AROUSAL—II
Moderator: Steve Henriksen, Ph.D.

1:15- Jerome Siegel, Ph.D. Ventral Brainstem, Sleep and Neuronal Injury

- *Review evidence for the physiological role of the ventral brainstem in sleep regulation. Contrast the effects of ventral midbrain lesions on neuronal degeneration to those seen after basal forebrain lesions. Discuss aspects of the ventral brainstem system and neuronal degeneration in other sleep-wake areas that may be relevant to the various manifestations of insomnia.*

1:45 Clifford B. Saper, M.D., Ph.D. Hypothalamic Lesions and Sleep Regulation

- *Review evidence for the relationship between cell-specific damage from lesions in and around the ventrolateral preoptic nucleus and sleep regulation. Discuss aspects of VLPO lesions and early gene expression experiments that may be relevant to the various manifestations of insomnia.*

2:15 Robert Greene, M.D., Ph.D. Adenosine, Basal Forebrain and Wakefulness

- *Review evidence that extracellular adenosine is a neuromodulator of basal forebrain cholinergic neurons, through which it promotes transition to sleep as wakefulness is extended. Discuss adenosine interactions with basal forebrain and preoptic/anterior hypothalamus that may be relevant to the various manifestations of insomnia.*

2:45	Giulio Tononi, M.D., Ph.D.	<p>Molecular-Genetic Correlates of Sleep and Waking</p> <ul style="list-style-type: none"> • <i>Review evidence that the transition from sleep to waking is accompanied in many brain regions by activation of c-fos and other immediate early genes, and that certain genes are upregulated primarily in either waking or sleep. Discuss how certain gene expression in wakefulness and sleep may be relevant to the various manifestations of insomnia.</i>
3:15	<i>Break</i>	
3:40	Larry D. Sanford, Ph.D.	<p>Conditioned Fear, The Amygdala and Sleep</p> <ul style="list-style-type: none"> • <i>Review evidence that the amygdala has a role in modulating brainstem neural mechanisms underlying alerting during sleep. Show how a conditioned fear model in inbred mouse strains may permit examination of genetic and neural mechanisms underlying the influence of anxiety on sleep. Discuss amygdala-sleep interactions that may be relevant to the various manifestations of insomnia.</i>
4:10	Una McCann, M.D.	<p>MDMA Use, Serotonin Neurotoxicity and Sleep</p> <ul style="list-style-type: none"> • <i>Review evidence that (+/-) 3,4-Methylenedioxymethamphetamine (MDMA, 'Ecstasy)—a popular drug of abuse—is a brain serotonergic neurotoxin that also produces functional abnormalities in sleep and waking. Discuss how MDMA and related drugs of abuse may be relevant to the various manifestations of insomnia.</i>
4:40	Panel	<p>Session Speakers Open Discussion</p>
5:30	Adjourn	

TUESDAY, SEPTEMBER 11, 2001

SESSION 3: CLINICAL NEUROSCIENCE OF MOOD DISORDERS AND INSOMNIA

Moderator: Allan I. Pack, M.D., Ph.D.

8:00	Husseini K. Manji, M.D.	<p>Neurobiology of Mood Disorders</p> <ul style="list-style-type: none"> • <i>Provide an overview of the neurobiology and pharmacology of depression and anxiety disorders. Discuss aspects of this neurobiology that may be relevant to the comorbidity of insomnia and mood disorders.</i>
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- 8:45 Gary S. Richardson, M.D. Insomnia and Physiological Arousal During Sleep
- *Review evidence that physiological arousal is an important feature of primary insomnia, and whether there is evidence of activation in CNS, ANS, thermoregulatory and/or endocrine correlates of insomnia. Discuss whether physiological activation is primary or secondary to insomnia.*

9:15 *Break*

- 9:30 Eric Nofzinger, M.D. Neuroimaging of Sleep States: Mood and Arousal
- *Review evidence that PET measures of regional cerebral glucose utilization show EEG arousal during sleep in specific cortical areas, and that changes in limbic and paralimbic functions from waking to REM sleep are different in normal and depressed patients. Discuss how regional differences in brain activation may be relevant to the manifestations of insomnia.*

Note: *Due to circumstances beyond our control, the meeting was adjourned at 10:00 AM. The following content is included in the final report but was not presented at the workshop:*

- Pierluigi Gambetti, M.D. Pathophysiology and Genetics of Fatal Familial Insomnia
- *Review the molecular neuropathology and genetics of human prion protein diseases involving alterations of sleep. Describe the neuropathology of fatal familial insomnia relative to sleep neurobiology. Discuss FFI and related prion diseases relative to other manifestations of insomnia.*