

BULLETIN

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President's Message

October of 1999 was a memorable month for the SRS. The World Federation of Sleep Research Societies (WFSRS) meeting in Dresden was packed with science and provided a very special venue to touch bases with our fellow travellers in sleep research world wide. SRS provided support to help 34 North American trainees to take part in the WFSRS meeting. One meeting format that was new to me was organized guided tours of posters on related topics. This type of small group discussion seemed quite effective. Congratulations to the WFSRS program committee and particular thanks to Hartmut and Renate Schulz for all their careful preparation of this wonderful meeting.

October also featured a smaller meeting organized in conjunction with the American Physiological Society by a committee chaired by Allan Pack. The topic of this meeting was: "Determinants of Vigilance: Interaction Between the Sleep and Circadian Systems." This very exciting meeting formed the basis for Dr. Pack's successful application for the 1999 SRS Training program support. As a consequence, SRS was able to support 31 additional trainees to attend this meeting. A very different format from our annual meetings, the single-tracked, focused program provided for an in-depth consideration of the topic. Might this type of meeting provide a template for SRS Sections to plan similar tightly focused conferences in the future? Food for thought...

Another richly rewarding October event was the distribution of revenues to SRS from our partnership ventures with the American Academy of Sleep Medicine. This partnership continues to flourish in congenial and productive ways.

As we move deeper into autumn with winter and the new year looming, it is important to look forward to opportunities that await and to take an active role in guiding our destiny. Each of

you, for example, will likely benefit by subscribing to the SleepRFA-L, a listserve put out by Michael Twery at NIH with bulletins regarding all announcements that have any relation to sleep or circadian biology research, including program announcements, requests for applications, and others. Dr. Twery goes to the effort of gleaning the critical announcements for us, locating those that may not mention sleep in the title, but have an interest in sleep. To join SleepRFA-L or view archives go to the following website: <http://list.nih.gov/archives/sleeprfa-l.html>. I urge all SRS members (particularly those in the US) to join.

Another way for SRS to guide its destiny is to become a more active society in voicing our needs and taking a "seat at the table" in organizations whose missions overlap ours. For example, the SRS executive committee provided feedback on behalf of the sleep research community to the Center for Scientific Review on its preliminary reorganization report. [Read our CSR response in this issue of the Bulletin.] Furthermore, SRS will be working with the National Center on Sleep Disorders Research (NCSDR) on a number of issues, perhaps partnering to organize a workshop to examine training and career issues in our field. To keep the NCSDR aware of SRS activities, SRS will also start presenting a report to the Center's advisory board and to the director on a continuing basis. Member suggestions to the Executive Committee are always welcome; remember, your Section Head is a member of the Executive Committee.

Finally, SRS internal activities are becoming much more effective, as we begin to utilize our resources fully and to implement the recommendations of the Vision2020 Taskforce (<http://www.srssleep.org/vision2020/finalreport.html>).

I end with wishes for a very joyous holiday season and a productive Y2K for all members of the SRS! Cheers!

Editor's Note

Readers of the Bulletin will notice our new format. We have moved the "production" of the Bulletin from Galveston to the central office. Mr. Lance Brink, SRS Administrative Coordinator is now responsible for the physical layout of the Bulletin. He, and Mr. Thomas Meyer, Communications Director

of the AASM, have given a more professional look to the Bulletin. There are other changes in store for the Bulletin, which we feel will result in a better newsletter. These will be detailed with the first issue of volume 6, our millennium volume. I certainly wish to extend my thanks to Lance for taking on this task.

Narcolepsy: A key role for hypocretins (orexins)

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The recent discovery of the genetic cause of canine narcolepsy is an exciting discovery for sleep research. Rather than review this work again for the Bulletin, we have received permission from Cell to reprint the mini-review by Jerry Siegel that appeared with the papers on the genetic work, ed.

Two recent papers have linked narcolepsy to dysfunction of the newly discovered hypocretin (Hcrt) (orexin) peptide system. The paper by Lin et al. (1999, previous issue of Cell) examined the genetic correlate of canine narcolepsy, using the well-characterized Doberman pinscher and Labrador retriever models. They found a deletion in the transcripts of the Hypocretin receptor 2 (Hcrtr2) gene in the narcoleptic Doberman and a different deletion in the receptor transcript of the same gene in the narcoleptic Labrador. Lin et al. speculate that these changes disrupt the proper membrane localization or transduction functions of this receptor. The paper by Chemelli et al. (1999, this issue of Cell) used a different approach to arrive at a similar conclusion. They created a knockout of the Hcrt gene in mice. The knockout mice had abnormalities of sleep control resembling aspects of narcolepsy. Together these two studies implicate dysfunction of the Hcrt system or systems closely linked to the Hcrts in the pathophysiology of narcolepsy. The implications of these findings can best be understood by reviewing the nature of narcolepsy and of the Hcrt system.

What is narcolepsy?

Narcolepsy is a disease affecting approximately 1 in 2,000 individuals (about 125,000 in the US) and usually develops in the second or third decade of life with symptoms progressing over a period of one or two years and then stabilizing. Narcolepsy is characterized by sleepiness and cataplexy, which is a loss of muscle tone triggered by sudden strong emotions such as laughter and sudden anger. Attacks of cataplexy are usually brief but in some narcoleptic patients can last for periods of minutes and be disabling. In contrast to sleep attacks, consciousness is maintained during cataplexy. In most narcoleptic patients, sleepiness rather than cataplexy is the more troublesome symptom. Narcoleptics go through life feeling the way most of us would feel if we had been awake for 24 hours. They awake refreshed from naps, but soon are sleepy again. Their nighttime sleep is

fragmented with less of the deeper stages of sleep.

Narcolepsy also has been reported in horses, cattle and dogs. Some cases of canine narcolepsy are sporadic and these dogs cannot be bred to produce narcoleptic offspring. Occasionally, entire litters are born that develop the symptoms of narcolepsy at 1-4 months of age and show both sleepiness and cataplexy. In the early 1970's, Dement, Mitler and their colleagues found that it was possible to breed these familial narcoleptic Doberman pinschers or Labrador retrievers. The disorder is transmitted in the Dobermans and Labradors as a single gene autosomal recessive trait with full penetrance.

The sleepiness of narcolepsy can be treated by a number of agents, such as amphetamine-like drugs and Modafinil, which increase arousal. Cataplexy is commonly treated with tricyclic antidepressants and by selective serotonin reuptake inhibitors. Nishino and colleagues have shown that the selective serotonin reuptake inhibitors as well as the antidepressants inhibit cataplexy in proportion to their activation of norepinephrine receptors. In contrast, prazosin, which blocks alpha 1 noradrenergic receptors, greatly exacerbates cataplexy in both dogs and humans. Cholinergic agonists and the cholinesterase blocker physostigmine also exacerbate cataplexy, consistent with a role of cholinceptive neurons in triggering muscle tone suppression. Thus the balance between the noradrenergic and cholinergic systems is a major factor in the control of cataplexy.

In normal individuals, postural muscles maintain some level of tone throughout waking and non-REM sleep. Only in REM sleep is muscle tone completely abolished. This suppression of tone prevents the motor programs generated in REM sleep from causing dangerous and sleep disrupting movements. The similarity between the atonia in REM sleep and the atonia in cataplexy, and the abnormally short latency to REM sleep onset shown by narcoleptics, have led to the hypothesis that cataplexy may represent a triggering, in waking, of the mechanism that normally functions to suppress muscle tone in REM sleep. Studies in the narcoleptic dog have supported this hypothesis and provided insights into the nature of the mechanisms controlling posture in waking. Recordings of brainstem neuronal activity in narcoleptic dogs have shown that cataplexy is linked to the activation of a population of cells in the medulla and pons that in normal animals is active only during REM sleep (Siegel et al., 1991; Siegel, 1994). During REM sleep and presumably during cataplexy, this pontomedullary system causes the release of glycine onto motoneurons, producing hyperpolarization.

At cataplexy onset, at the same time as glycine begins to be

released, the norepinephrine-containing neurons of the locus coeruleus, which are normally continuously active in waking, abruptly and completely cease discharge (Wu et al., 1999). They also cease discharge in REM sleep. Norepinephrine released from these neurons is known to facilitate motoneurons (Figure 1). Thus, a combination of active inhibition and disfacilitation (reduced excitatory input) appears to underlie both cataplexy and the muscle atonia of REM sleep.

What are the hypocretins (orexins)?

In 1998, de Lecea et al., using directional tag PCR subtraction, described a hypothalamus specific mRNA that encoded "preprohypocretin," a putative precursor of two peptides, Hcrt1 and 2. They named these peptides hypocretins (Hcrts) to indicate their hypothalamic localization and similarity to the gut hormone secretin. At about the same time, Sakurai et al. (1998) were searching for ligands for certain cDNA sequences that resembled G protein coupled receptors but had no known ligands, i.e. orphan receptors. They identified peptides that bind to and activate two related receptors. Because they found that these peptide ligands stimulated food intake, they named them "orexins" after the Greek word for appetite. The peptides described by de Lecea et al. and Sakurai et al. are identical.

Anatomical studies determined that the somas of the Hcrt-producing cells were restricted to the hypothalamus and concentrated in the perifornical nucleus and in the dorsal, lateral and posterior hypothalamus. The mRNA for the Hcrts is expressed by embryonic day 18 in rats and increases dramatically after postnatal day 21 (de Lecea et al., 1998). Although the cell bodies of Hcrt producing neurons are entirely restricted to the hypothalamus, they have widespread axonal projections. In addition to dense hypothalamic projections, the limbic system, thalamus, subthalamic nucleus, substantia nigra, raphe, locus coeruleus,

ventral tegmental area, medullary reticular formation, nucleus of the solitary tract and other brainstem regions are innervated by these cells (Peyron et al., 1998). The neocortex also receives projections. Hcrt receptors are distributed throughout the innervated regions with a striking segregation of the two receptor types within rat brain (Trivedi et al., 1998). Hcrt2 mRNA is mainly expressed in cerebral cortex, nucleus accumbens, subthalamic and paraventricular thalamic nuclei and anterior pretectal nucleus. Lin et al (1999) implicate the Hcrt2 in canine narcolepsy.

Physiological studies showed that Hcrt release raises cytoplasmic calcium levels by opening plasma membrane channels and increases the release of both gamma amino butyric acid (GABA) and glutamate from axon terminals (van den Pol et al., 1998). Hcrt neurons have close and reciprocal connections with hypothalamic neurons containing neuropeptide Y (NPY) (Horvath et al., 1999), which strongly stimulates appetite, suggesting that Hcrt neurons have a role in feeding and metabolic control. The entire lateral hypothalamic region in which the Hcrt neurons are embedded has long been thought of as an appetite control "center."

Pharmacological and physiological studies indicate that Hcrt neurons have a role in appetite (Sakurai et al., 1998). Hcrt-producing cells express leptin receptor immunoreactivity (Horvath et al., 1999). Insulin-induced hypoglycemia greatly increases the level of the Hcrt precursor protein. Leptin treatment decreases Hcrt levels. Genetically obese mice have downregulated Hcrt gene expression. Microinjection of Hcrt and in some cases intracerebroventricular administration triggers feeding (Sweet et al., 1999) and increases metabolic rate.

The link between narcolepsy and the hypocretins

The two apparently unrelated topics of a putative lateral hypothalamic feeding hormone and a disease characterized by episodes of sleepiness and sudden losses of muscle tone have now been forever united by the work of Lin et al. (1999) and Chemelli et al. (1999). The narcoleptic dogs studied by Lin et al. have clear episodes of cataplexy, disturbed sleep and evidence of sleepiness resembling that shown by human narcoleptics. They are also similar to human narcoleptics in their response to drugs that exacerbate and ameliorate cataplexy and sleepiness.

It remains to be determined if the Hcrt gene knockout mice created by Chemelli et al. have the features of human and canine narcolepsy. These mice lack the Hcrt peptides, in contrast to the dogs, which have mutations in the Hcrt 2 receptor. Although they have periods of "behavioral arrest" it is not yet clear if these include periods of cataplexy or if they are all direct transitions from waking into REM sleep. The triggers for these episodes differ from those in the dogs, with emotional excitement associated with food intake not being a common instigator of attacks in the mice. It may well be that an identical knockout in a dog would produce symptoms similar to those seen in the narcoleptic Doberman and Labrador, but that the brain of the mouse does not contain the machinery required for full expression of the syn-

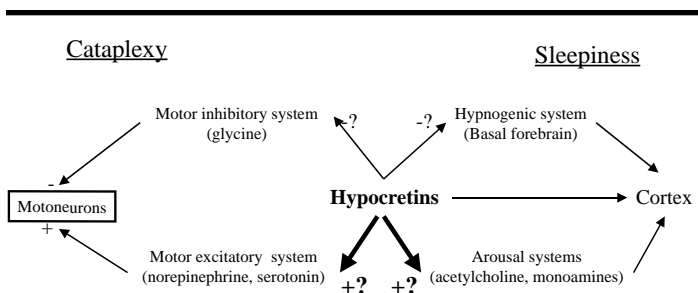


Fig. 1—Possible role of the hypocretins (orexins) in the pathology of narcolepsy. The hypocretins (orexins) are known to project to brainstem regions linked to motor inhibition as well as to locus coeruleus (norepinephrine), raphe (serotonin) and laterodorsal tegmental nuclei (acetylcholine) and ventral tegmental (dopamine) neurons. They also project to forebrain regions including posterior hypothalamus (histamine), septal nucleus and diagonal band (acetylcholine) neurons and have major projections to the amygdala and basal forebrain hypnogenic regions. Loss of function of the hypocretin system could cause cataplexy by disfacilitating the brainstem's motor excitatory systems or by disinhibiting the brainstem's motor inhibitory system. Loss of function of the hypocretins could increase sleepiness by disfacilitating the cholinergic and aminergic arousal systems or by disinhibiting the forebrain's hypnogenic systems. The few physiological studies done to date suggest that the hypocretins are usually excitatory; therefore these two possibilities are highlighted in the figure.

drome seen in humans and dogs. Conversely, an Hcrtr2 knockout mouse might more closely mimic the symptoms seen in dogs and humans. Sleep is disrupted in the Hcrt knockout mice although it is not clear that they are "sleepy." Finally the pharmacologic response of these symptoms is not reported in the Chemelli et al. paper. Clearly much work remains to be done to fully characterize this new model of narcolepsy. Nevertheless, the presence of sleep onset REM sleep periods and disrupted sleep in both dog and knockout mouse provides strong support for the proposed involvement of Hcrt in narcolepsy.

How does the finding of Hcrt linkage explain the symptoms of narcolepsy?

A remarkable link appears to exist between the anatomy of the Hcrt system and the triggering of cataplexy. Peyron et al. (1998) report that the densest extrahypothalamic projection of the Hcrt system is directed at the locus coeruleus. As outlined above, cessation of activity in locus coeruleus cells precedes and accompanies cataplexy, and narcoleptic dogs have a relatively low rate of locus coeruleus discharge (Wu et al., 1999). In normal animals, locus coeruleus cells never cease discharge during waking. Hcrt administration has been shown to greatly increase c-fos labeling in locus coeruleus neurons (Date et al., 1999), an indication that Hcrts increase discharge in locus coeruleus neurons. Thus it can be argued that a malfunctioning Hcrt system, by removing a source of excitation from the locus coeruleus, would increase the propensity for cataplexy. However, the Hcrt2 receptor that is mutated in narcoleptic dogs is not present at high levels in the locus coeruleus of rats. If this is also true in the dog, one may hypothesize that the Hcrt2 receptor mutation leads to a more widespread loss of Hcrt function than would be caused by Hcrt2 receptor malfunction alone. This may occur through disturbed feedback regulation or degeneration of Hcrt neurons resulting in a disfacilitation of locus coeruleus cells mediated by diminished activation of the Hcrt1 receptor.

Although we now understand key elements of the system responsible for cataplexy, the neurons responsible for the sleepiness of narcolepsy have not been identified. Several populations of cells known to increase arousal or increase sleepiness exist. Reduced excitation of the noradrenergic cells of the locus coeruleus, serotonergic cells of the raphe, dopaminergic cells of the hypothalamus and mesopontine region or histaminergic cells of the posterior hypothalamus, could reduce arousal levels. Reduced excitation of cholinergic neurons of the basal forebrain and brainstem would also impair behavioral and EEG arousal.

Conversely, the Hcrts could directly or indirectly inhibit sleep active neurons in the basal forebrain, amygdala or the hypnogenic regions of the nucleus solitarius. If this were the case, dysfunction of these projections would increase sleepiness. If the Hcrts have a role in monoamine and acetylcholine release similar to the role they have been shown to have in GABA and glutamate release, Hcrt hypofunction could cause the accumulation of dopamine and the upregulation of several receptor types that is

observed in the narcoleptic dogs. It is significant that the hypocretin neurons have direct projections to all of the arousal and sleepiness modulating cell groups mentioned above.

Recent work has shown that there is neuronal degeneration in limbic forebrain regions in the narcoleptic dogs. This degeneration peaks before symptom onset (Siegel et al., 1999). Degeneration is maximal in the amygdala and septal nuclei and is also elevated in the diagonal band, thalamus and hypothalamic regions. These areas receive a moderate to heavy Hcrt innervation. Tafti et al. (1996) have reported increased expression of major histocompatibility class II molecules in brain microglia of narcoleptic dogs, with a time course parallel to the degeneration we see, consistent with direct or indirect immune activation. Could the Hcrt2 gene mutation be linked to these degenerative changes? The human Hcrt precursor gene is located at chromosome 17q21-22, a gene locus that has been implicated in a series of neurodegenerative disorders (Basun et al., 1997), suggesting a possible role for Hcrts in other neurodegenerative diseases. An intriguing clue to the possible role of Hcrts in degeneration comes from the recent report of Ichinose et al. (1998). They found that Hcrt2 induced an outward current in peritoneal macrophages, indicating that the Hcrts can modulate macrophage functions through the activation of Ca²⁺ dependent K⁺ channels. It remains to be determined if the Hcrts have similar action on brain microglia. However, such a role could unite the loss of Hcrt function with the postulated but unproven immune link to narcolepsy.

Malfunction of the Hcrt system might be expected to affect several systems not implicated in sleep and arousal control. Van den pol has shown that Hcrt neurons strongly innervate the spinal cord. The innervation is targeted to dorsal regions involved in autonomic and pain control and may explain the profound analgesia produced by lateral hypothalamic stimulation. Hypofunction of this system might be involved in pain syndromes, but there has so far been no report of any linkage of narcolepsy to altered pain perception.

A simplistic prediction based on the role of Hcrts in appetite stimulation would be that narcoleptics should have a gross abnormality of food intake resulting in anorexia. However, there is no evidence for anorexia in unmedicated narcoleptics. Conversely, although there may be some modulation of narcoleptic symptomatology as a function of food intake, there is no strong evidence for the major change in symptoms that would be predicted by the effects of hypoglycemia on Hcrt neurons. Similarly, hypofunction of the nucleus accumbens, a site for reward integration, might suggest a syndrome of anhedonia in narcoleptics, but none has been reported. However there is evidence for higher rates of depression in narcolepsy. This might be explained by reduced Hcrt excitation in the nucleus accumbens.

In general the deficits seen in animals with gene knockouts must be thought of as due to a combination of loss of gene function

combined with the body's compensatory response to the loss. Receptor upregulation, synaptic sprouting, biochemical changes within the affected cells, loss of trophic factors, immune interactions and other changes may combine to produce the resulting phenotype. NPY neurons are adjacent to and have close synaptic interactions with Hcrt cells. NPY administration produces a more potent activation of food intake than does Hcrt administration. However, the NPY knockout mouse has normal weight regulation and response to food deprivation. On the other hand, these mice are prone to seizures and have elevated responses to leptin (Erickson et al., 1996). It may well be a similar reorganization of brain systems interacting with Hcrt neurons that causes the symptoms of narcolepsy, rather than the immediate effects of the Hcrt receptor malfunction or Hcrt disruption.

Relevance to human disease

Mutations of the Hcrt system may be responsible for some proportion of human narcolepsy cases. However, it is unlikely that most human narcoleptics have a mutation in their Hcrt or Hcrtr genes. Most narcoleptics have no narcoleptic relatives, ruling out the autosomal recessive mode of inheritance seen in the dogs. The typical onset of symptoms in the second decade of life or later suggests that damage has occurred to a normally functioning sleep and motor control system. Approximately 75% of the pairs of identical twins examined are discordant for the disease, suggesting that environmental factors are critical in the triggering of human narcolepsy.

More than 85% of all narcoleptic patients with cataplexy share a specific HLA allele, HLA DQB1*0602, compared with 12 to 38% of the general population (Mignot 1998). Because of the role of HLA gene products in immune regulation, because most HLA linked are autoimmune in nature and because of the evidence that environmental triggers might be involved, it has been speculated that narcolepsy might be an autoimmune disorder. An obvious question is whether there is evidence for an immune attack on the Hcrt2 receptor in human narcolepsy. Since receptors are continuously regenerated, any immune attack that affected only the receptors would have to continue for the duration of the disease. No such autoimmune process has so far been detected. Alternatively, irreversible damage to axon terminals or to the hypocretin neurons themselves, creating the equivalent of an Hcrt knockout, might cause the disorder. The deficit in human narcolepsy may also be downstream of the Hcrt system. For example, immune mediated damage to neurons or receptors in the locus coeruleus, amygdala or basal forebrain sleep related regions might produce the syndrome even with normal function of the Hcrt neurons and the Hcrt2 receptor.

Therapeutic implications

Current treatments for narcolepsy provide some symptomatic relief at the expense of substantial side effects. The nature of the altered function caused by the Hcrt2 receptor mutation in the dogs is at present unclear. If the mutations cause a moderately diminished functional response to their ligand, administration of

Hcrts might improve symptoms. Similarly, in the knockout mouse, the effects of the loss of Hcrt might be reversed by Hcrt administration. If similar pathologies exist in humans, the same treatments could be effective. However, since Hcrt has been reported to increase eating, metabolic rate and gastric acid secretion, and Hcrts have a role in the control of anterior pituitary hormones and pain regulation, a large number of brain systems would likely be affected by Hcrt administration. The possibility of effects on the immune system should also be considered. Moreover, Hcrts produce "wet dog shakes" in rats, an indication of stress or anxiety, and high doses produce seizures in rats (Ida et al., 1999). Since the Hcrt system is strongly connected with the noradrenergic and serotonergic systems, themselves diffusely projecting, both therapeutic and deleterious effects could be mediated by secondary alteration in the activity of these aminergic systems. The development of specific Hcrt agonists might reduce these problems. Since some of the most successful neuroactive therapeutic agents manipulate the widely projecting aminergic systems, there is reason to hope that manipulation of the Hcrt system will also lead to useful drug therapies for narcolepsy.

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Student BITS (Brief Insights for Training in Sleep)

For this issue, we are fortunate to have Sean P. A. Drummond, veteran trainee extraordinaire, detail the ways that we can both benefit from and contribute to the Sleep Research Society as an entrance to our professional lives. Sean has served SRS in a number of capacities, including as a former member and Chair of the APSS Trainee Program Committee and former SRS Trainee Member-at-Large, and has contributed to the ongoing high quality of trainee programs and participation in the SRS.

The Student BITS segment is an ongoing forum for issues pertaining to sleep and to the training and retention of sleep scientists, from a trainee's perspective. All trainees, undergraduate, graduate, or postdoctoral, who are interested in submitting an article for Student BITS are invited to contact Monica Eiland, Assistant Editor, SRS Bulletin: Student BITS: email: meiland@ucla.edu; phone (818) 891-7711 ext 7380; fax: (818) 891-7711 ext 7380; regular mail: Neurobiology Research 151A3, Sepulveda Veterans Administration Medical Center, 16111 Plummer St., North Hills, CA 91343.

The Joys of Participation

By Sean P. A. Drummond - drummond@rohan.sdsu.edu

When I first agreed to write a column on the virtues of participating in the SRS as a trainee, I thought it would be easy. After all, I've participated in many ways throughout the past several years and found it both an invaluable experience and utterly rewarding. However, as I started writing, I realized that it is no easy task to convince a group of time-strapped trainees to give up valuable free time in the name of the Greater Good. So, I decided to make a list of the reasons I chose to help out and the benefits I derived from doing so (in the end, they are one in the same) followed by the ways you can participate in the SRS.

Benefits of participation:

1. Networking with senior investigators. In almost every role you can play in SRS affairs, you will be fortunate enough to interact closely with senior members of the society. This, of course, has a couple of benefits. First, you are able to learn about many aspects of "professional development" from them. Second, it is unfortunate (but true) that in today's academic and clinical arenas the more people you know, the more likely you are to have options in the job market and allies on review committees.

2. Gaining friendships with peers. This is one of the most rewarding parts of participating, in various ways. The sleep field has many wonderful trainees. Getting to know many of you over the past few years has been enjoyable and enriching.

3. Valuable organizational experiences. As I look around me, I see that no matter what career path we follow or job we take, there will almost inevitably be some administrative duties involved. Opportunities exist within the SRS for trainees to serve on committees (e.g., Trainee Program Committee and CARE). These experiences can teach you not only how to work well with a diverse group individuals, but also how to organize such a talented group to achieve a common goal. I believe this is not only important for those dreaded committee assignments your department chair will burden you with one day, but shall prove equally useful if one day you find yourself running a lab that consists of more than yourself and your polygraph.

4. See the inner workings of a national society. This one may not turn everyone on, but I found it fascinating to participate, as the Trainee Representative, in SRS Executive Board conference calls and annual meeting at APSS.

5. Duty. This is perhaps the most difficult reason to preach and likely the most difficult to accept. Nonetheless, I personally feel undying gratitude to the SRS. Since 1991, I have received several Travel Awards (now Merit Awards) to attend conferences everywhere from the Bahamas to Toronto. Furthermore, I am sure some of you reading this received help in traveling to either France in 1991 or Germany this year. In addition to travel awards, the SRS and AASM allow trainees to gain experience and exposure by Chairing symposia at the annual APSS conference. They also sponsor a daylong educational program at APSS designed by and for trainees (i.e., the Trainee Symposia Series). I venture to guess that few, if any, other professional societies treat their trainees so well. All that is asked in return is an hour or so volunteering to run a slide projector at the conference - a small price to pay!

6. Making a difference. The ways in which a trainee can participate in the SRS are not hollow gestures and frivolous exercises designed to keep us happy and quiet. When you serve on the Trainee Program Committee, or even provide the committee a program suggestion, you are literally helping shape the educational experiences of over 170 fellow trainees at the APSS conference. As the editor of the Trainee Email Network or this very Student BITS column, you help disseminate valuable information to your fellow trainees and those considering joining the field.

OK, now I've outlined the multitude of ways that participation in the SRS can be both enjoyable and rewarding. While those rewards certainly don't give you more free time, I hope at least a few of you reading this are wondering, "Gee, how can I participate?" Well, I'm glad you asked. There are more ways than ever to participate in the SRS as a trainee. Some take only a matter of minutes, while others require a few hours per week for a few months at a time. I encourage you to peruse this list and pick one or two that seem doable - and do them.

1. High School Essay Contest. As most of you know, in this annual contest (dreamed up by Tom Kilduff, Ph.D.), high school students write essays on any topic in sleep they wish. Trainees can help in two ways: You can send a letter and entry form to your local high school and/or alma mater high school. You can serve as a judge for the essays that are submitted. Time requirement: 10 minutes to mail a letter; 1 hour to serve as a judge. Added bonus: in the past, judges have all received a coveted Sleeping Brain t-shirt, courtesy of Michael Chase, Ph.D. and the Brain Research Institute (past performance is no guarantee of future results). For details, watch the T-net.

2. Trainee Email Network (T-net) editor. This email bulletin board is the brainchild of Michael Perlis, Ph.D. The editor simply keeps track of the list of all sleep trainees' emails and sends out useful messages on an occasional basis. Surely, you have seen the emails from the current editor, Katie Sharkey. If not, send her an email to get signed up. (ksharkey@rush.edu) Time requirement: 5-10 minutes per week, max.

3. Trainee Web page. This was originally established by Tim Hays, Ph.D. and Michael Chase, Ph.D. Trainees can contribute content to the Web page (links, articles, job postings, etc). An adventurous trainee may even consider assuming the job of maintaining the Web page. Email Katie Sharkey for more details on either.

4. Student BITS. This column started a few years ago with Tim Hays, Ph.D. as the founding editor. If you are reading this right now, you have an idea what the column is all about. You can participate through this vehicle in two ways: as a contributor to the column or as editor of the column (who is actually a SRS Bulletin assistant editor, currently Monica Eiland). Either way, you get a nice item for your CV in addition to helping out the SRS. Time requirement: 2 hours to write a column (if you're a slow typist like me); 1 hour/week as editor.

5. Chair of Symposia at APSS. This brand of participation is unique in that it is not dependent on the trainee's desire alone. Rather, one must be asked to serve in this capacity. The way in which this happens is a bit of a mystery to me. Nonetheless, if you are asked to be a symposia Chair, it is an excellent way to meet some of the top researchers in your particular specialty. Time requirement: about 1 hour at the APSS conference.

6. Suggestions for the Trainee Symposia Series program. Every year as the Trainee Program Committee begins to organize the Trainee Symposia Series agenda, they send out an email over the T-net asking for suggestions for the program. This is one of the best ways to get some of your educational needs met at the APSS conference. Trust me, the Committee takes these suggestions very seriously. In the past, we have incorporated your suggestions into every facet of the program. The flip side of suggesting program items is filling out the evaluation forms after attending the Trainee Symposia Series. The Committee takes the evaluations quite seriously, as well. Time requirement: 10 - 15 minutes on each end.

7. Presenter at the Trainee Symposia Series. Many fine trainees have presented talks during past Trainee Symposia Series. You can volunteer for next year's program. Time requirement: ~20 minutes for the presentation + preparation time. Again, email Katie Sharkey for details.

8. CARE (Committee for Animal Research Ethics). This committee, chaired by Adrian Morrison, D.V.M., Ph.D., started up just before the APSS conference in 1999. Placing trainees on CARE is just another example of how the SRS values us. Perhaps trainees will also be included in future SRS committees as well. For details about CARE, you can email Dr. Morrison at armsleep@vet.upenn.edu.

9. Trainee Program Committee. This is one of the more time consuming, but also one of the more important ways to participate as a trainee. This committee fully designs, implements, and

evaluates the Trainee Symposia Series at APSS. We are fortunate that the SRS and AASM believe in the importance of the trainees enough provide us an entire day on the APSS conference schedule. The willing participation of so many senior members of our field (thank you to all of them - see last issue's column by Katie Sharkey) further adds to the value of the Symposia Series and thus the role of those who develop it. My service on the first three of these Committees provided every benefit listed above - and then some. Time requirement: 2-3 hours/week, November - June, with a few weeks here and there of increased time.

10. Trainee Representative (aka Trainee Member at Large).

This represents the pinnacle of participation. The Trainee Rep has many responsibilities, including Chair of the Trainee Program Committee. While the work load for this position is the greatest of any listed here, the rewards are also the greatest. I believe that in the past the time commitment of this position has turned away some potentially excellent candidates. If you are considering running for Trainee Rep, please do not allow yourself to be intimidated by the workload. Over the past three or four years, as attempts have been made by Dale Edgar, Ph.D. (SRS Program Chair for Trainees), Michael Perlis, Ph.D. (SRS Assistant Director of Training), and the last few Trainee Reps (myself, Tim Hays, Ph.D., and Katie Sharkey), to increase the number of trainees actively participating in the SRS, the workload has decreased. I would hate for good candidates to choose not to run for lack of time. Personally, I think of my time as Trainee Rep as one of my most fulfilling and useful endeavors in my nascent career.

11. Vote. The trainees themselves elect the Trainee Rep via mail-in ballot. In the past few years, voter turnout has been in the 50% range - better than your average U.S. Presidential election. I encourage all trainees to vote for this important position in the future. Time commitment: 5 minutes.

12. Future: While I have no knowledge of anything specific, history tells us that the SRS will no doubt find new ways for trainees to participate in the future. Keep an eye out for and take advantage of them when they arise. I would like to take this opportunity to suggest two possible avenues where trainees could both be useful and gain valuable experience: as reviewers for APSS abstract submissions and as a member of the APSS Program Committee. Now, I realize that both of these are quite ambitious - and not entirely up to the SRS alone - but I can dream, can't I?

Let me close by thanking you for reading this far. I truly believe that the SRS is a great society for trainees, and we would be foolish to not take advantage of the opportunities presented to us. Please consider volunteering, or at least providing some input. Every contribution enriches the Society - and you!

Sean P. A. Drummond is currently a Clinical Psychology Intern at the Tucson V.A. Medical Center in Tucson, AZ and will very soon need a postdoctoral position from which he can continue to be a participating trainee! Sean can be reached at: Southern Arizona VA Health Care System, Mental Health Care Line (4-116B), Tucson, Arizona 85723, (520) 792 1450 x5744, email: drummond@rohan.sdsu.edu.

Graduate and Post-Doctoral Fellowship Positions

CWRU and the Center for Sleep Education and Research has been awarded an interdisciplinary NIH Training Grant in the field of Sleep Medicine Neurobiology and Epidemiology. Areas of faculty interest include the functions and ontogeny of sleep, functional genomics, neuropharmacology and toxicology, pediatric and adult sleep physiology and psychology, cardiopulmonary control, and educational demonstrations in the teaching of sleep and chronobiology. Pre doctoral (Ph.D.) and post-doctoral positions are available. Appointment, stipend, tuition, and salary are based upon NIH guidelines, and appointments are intended to be for at least two years.

Send research interests, curriculum vitae, and contact information to: Kingman P. Strohl M.D., Department of Medicine, 111J(W), Pulmonary and Critical Care Medicine, 10701 East Blvd., Cleveland, Ohio 44106; e-mail: kps@po.cwru.edu

Women and minorities are strongly encouraged to apply.

A Sleep Expert in Court: Musings Following a Court Appearance

Rosalind Cartwright - rcartwri@rush.edu

The charge was murder. The defense was sleep walking. Being a sleep expert witness in the court room is very unlike our experience of plying our trade in the laboratory, classroom or the consulting office. When we research, teach, or even explain a sleep disorder to a patient we are not challenged on our facts nor are these disputed by an expert for the "other side". Court is an adversarial environment different from our usual venues. Not that there are no legitimate areas of debate in our field. We all have enjoyed disputing points of view with colleagues at APSS meetings, but here the stakes are different: the price may be not just a blow to our ego but the life of the defendant.

If we accept that there is a sleep disorder in which a person can commit an act of violence resulting in the death of another person but not be responsible for that act due to the state of mind (brain) at that time not being one of waking, conscious awareness, then our first task is to define what that state is, and how it differs from the sleep that precedes and waking that follows it.

What can a person see, feel, hear, remember while sleep walking? Can they recognize faces, feel cold, pain, hear someone scream, behave as if they remember where to find things, yet have no memory for these events when fully awake? All of these questions were raised at a recent trial and were answered differently by the sleep experts for the prosecution and the defense. Just how complex can the behavior be without it indicating that the person is awake and therefore responsible? How long can an episode last? These too, were responded to differently by the experts. Will a sleep study conducted after the fact have the sensitivity to discriminate the true parasomnia patient from the motivated murderer? How many nights would it take and what signs would be accepted as indicative of this disorder? How does a person who is sleep walking get out of this state? What functions return in what order? Just how do we make the diagnosis of a patient, if experts differ in their answers to these questions, and, if there is no firm answers, do we have any business being in court acting as an expert witness?

These are all good questions and I have asked them of myself since testifying and would now like to share some of my answers with you and ask for your comments.

Now that there are over 300 cases of sleep related violence in the literature (see Sleep 1995, as well as the forensic literature), and goodness knows how many more in the world that have not come to our attention (Ohayon's recent epidemiological study puts the rate at 2.1%), we can begin to draw a general descriptive picture

of this state.

- The person can see well enough to orient in space...travel long distances by car, bike or running, but they do NOT recognize faces and do not speak.
- They do not feel pain, cold, or hear shouts or respond to their own name for some period of time.
- The motor skill behaviors can be relatively complex and coordinated, e.g. changing clothes, cooking, operating a car.
- An episode can last an hour or more without full awareness which usually returns gradually.
- The behavior can be quite "out-of-character" with their waking personality and usual behavior.... attacking a loved one, being enormously strong and vigorous.
- The sleep studies often show sleep that is much lighter (in terms of response to sound stimuli) than that described as characteristic of their pre-episode sleep and may not show the hypersynchronous delta "sign" prior to an arousal.

If the sleep studies do not have specific traits we can point to, and if the person's state and conditions can not be replicated after the fact, have we any business being in court as an expert witness in such a case? For myself, I have to answer "yes". The sleep studies may be corroborative if not definitive when added to the presence of a family tree showing a strong history of parasomnias in the relatives, a childhood history of previous episodes, a documentation of a recent period of stress leading to short and disrupted sleep, a lack of psychopathology or evidence of a seizure disorder, and most important, if there is not motivation for the attack.

We have a way to go to convince the public, the juries, and each other that we have the knowledge to make a judgement in such cases when our field cannot as yet give a definitive diagnosis from the PSG. However we can have reasonable clinical certainty using all we know from our own experience and that of our colleagues who have published their cases. But you may ask why do it? For myself I have two motives: one is the opportunity to learn more about this disorder, to begin to put together the picture of what areas of the brain are acting as they do in waking, and those that appear to still be asleep. (The fact that the localization of the spatial visual system is different from that for face recognition for example , supports the description of the sleep walking behavior in several cases I have dealt with). The other reason is the humanitarian one. I feel I owe it to someone afflicted with a sleep disorder that is so little understood to do what I can to share what I know. Would I prefer if we could do this as an expert for the judge rather than for one side or the other as has been suggested by the AAAS as the proper role for scientists in court, you bet! Should we take a position on this ? I invite your responses.

Phil Gehrman - pgehrman@ucsd.edu
2000 SRS Trainee Representative - Elect

Every year for the past seven years, the Sleep Research Society has sponsored an essay contest for high school students. The contest is aimed at raising awareness of the importance of studying sleep among high school students and in the community. Essays up to 1000 words in length are solicited from students from a variety of sources. Last year, students found out about the essay contest from: teacher publications (20%), internet postings (33%), information sent to high schools from SRS members (18%), and other sources (29%). A total of 282 entries were received, representing 51 high schools in 22 states and 1 Canadian province. Every entrant receives a "Sleeping Brain" T-shirt and their teachers receive a copy of Basics of Sleep Behavior and a syllabus designed to help them incorporate sleep-related topics into their curriculum. Up to five essays are picked to receive certificates of merit and cash awards of \$250. The high school that each winner attends will also receive a free copy of the Encyclopedia of Sleep and Dreaming (Carskadon, ed., New York: Macmillan, 1992, 630 pages). Information and contest rules can be found on the internet at: http://www.srssleep.org/essay_rules.html. You should be receiving a mailing that contains information that you can forward to teachers and/or schools to promote the contest. If you need additional information or if you would like to participate as a judge for this year's entries, you can contact me at pgehrman@ucsd.edu. We appreciate your support of the contest.

Let Sleeping Dogs Lie?

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One-third of the human lifetime is consumed by sleep, yet the biological function and genetic basis of sleep remain unknown. A genetic approach to narcolepsy might someday afford insight into the molecular basis of sleep control. Narcolepsy is a neurological disorder distinguished by a life-long dysfunction of wake and rapid eye movement (REM) sleep mechanisms. The main manifestations are constant sleepiness and REM-related attacks of loss of motor tone (cataplexy, sleep paralysis) or dreamlike experiences called hypnagogic hallucinations (Mignot et al., 1993). Narcolepsy plagues 100,000 to 150,000 Americans. The pathophysiology underlying narcolepsy continues to be a mystery. Discovery and studies of narcoleptic-like conditions in dogs interest scientists because progress in treatment of human narcolepsy could follow from studying animals suffering from an analogous disease.

Does man's best friend truly hold the key to unlocking the mysteries of narcolepsy, a debilitating human disease? Genetic transmission in several canine breeds has been discovered to be autosomal recessive with full penetrance, and the gene has been named *canarc-1*. Scientists believe that, in humans, the DQA1 0102 and DQB1 0602 alleles of the major histocompatibility complex (MHC) are the susceptibility genes for narcolepsy. Though there is still some disagreement among scientists as to the mode of transmission of narcolepsy in humans, most studies support a multifactorial mode of inheritance; others suggest a single dominant gene (Baker et al., 1982). Both of these possibilities differ from the autosomal recessive mode of inheritance that has been established in Doberman pinschers and Labrador retrievers.

There is no such thing as a perfect model for a human disease. So, are scientists barking up the wrong tree by using canine narcolepsy as a prototype for narcolepsy in humans? Studies have proved that cataplectic attacks in dogs can begin as early as three weeks of age in homozygous animals (Mignot et al., 1993). Severity of symptoms increases until five or six months of age, when, at this time, it levels off. Narcoleptic symptoms in canines heighten at the age of six months, the time when the dog reaches sexual maturity; similarly, the development of narcolepsy in humans frequently reaches its climax around the time of puberty. Symptom severity is independent of sex and decreases slowly with old age. This evidence demonstrates that the natural history of the illness in dogs parallels the evolution of the disease in humans (Mignot et al., 1993).

Other similarities between human and canine narcolepsy have been observed. Human narcolepsy can begin before puberty and is seen in children as young as age six, while cataplexy is noted in some animals that are homozygous for *canarc-1* as early as age three weeks. Cataplexy often improves with age in both humans and canines. One difference between canine and human narcolepsy is that canines are usually more affected by cataplexy than human patients; most narcoleptic human patients rarely exhibit cataplexy.

As stated previously, the human disorder appears to be a multi-genic illness involving predisposing genes for the disorder that are expressed in an autosomal dominant manner. It has been discovered that heterozygosity of *canarc-1* might predispose to narcolepsy. By using specific combinations of drugs, it is possible to provoke short narcoleptic attacks in animals that otherwise show no symptoms (asymptomatic) but are heterozygous for the *canarc-1* gene. The finding that heterozygosity of the *canarc-1*

gene might predispose to narcolepsy supports the involvement of a gene equivalent to canarc-1 in some forms of human narcolepsy (Mignot et al., 1993).

Is the field of medicine going to the dogs? Major advances in the management and treatment of narcolepsy in humans would almost certainly result from studying canines plagued by this analogous disorder. In a trial with a female toy poodle, attacks were continuously produced by small bits of meat. Then, the drug imipramine hydrochloride was given, and following its administration, cataplectic attacks induced by meat were less regular and of shorter periods of time. It seems clear that like cataplexy in humans, canine cataplectic attacks improve with imipramine, or similar drugs (Mitler et al., 1974).

Canine narcolepsy is the only known single gene mutation affecting sleep state organization as opposed to circadian control of behavior (Kadotani et al., 1998). Slow-wave sleep and rapid eye movement sleep are regulated by circadian processes. From a genetic standpoint, far less headway has been made in the non-circadian aspects of sleep regulation. The molecular cloning of the canarc-1 gene that causes narcolepsy in dogs may lead to a better understanding of the molecular basis and biological role of sleep (Kadotani et al., 1998). Perhaps scientists are barking up the right tree after all.

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The Adolescent Sleep Crisis

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Adolescent sleep habits are famous and infamous. Staying up late, sleeping as late as possible, and napping in class have all been attributed to teenagers' chosen lifestyles. Research has

shown, however, that biology plays a role, too. Adolescents' altered sleep patterns often lead to sleep deprivation, but steps can be taken to ameliorate this damaging condition.

Humans often overlook their biological need to sleep. This leads to sleep deprivation, a condition detrimental to the mind, body, and society. Mood, motivation, awareness, coordination, and memory are all negatively affected by sleep deprivation (Caldwell, 1997). Additionally, in a report for the National Commission on Sleep Disorders, Dr. Damien Leger calculated that in 1988 sleep-related accidents cost the U.S. \$56.02 billion and 24,318 lives (as cited in Coren, 1996).

Sleep deprivation is a major problem, especially for adolescents. Sleep Thieves author Stanley Coren writes that surveys consistently show "more than half the teenagers studied wish that they had more time for sleep" (pp. 120-121).

One reason adolescent sleep deprivation is so prevalent is the fallacy that teenagers need less sleep than when they were children. In fact, the physical and psychological changes of adolescence demand about nine hours of sleep each night (Maas, 1998). However, surveying 3,120 high school students, Mary Carskadon and Amy Wolfson (1996) found a mean sleep time of 7 hours and 20 minutes. Furthermore, their figures reported 26% of the students slept less than 6.5 hours a night, while only 15% slept an appropriate 8.5 or more.

Why are so many adolescents sleep-deprived? Previously, it was believed that only social factors were to blame. However, research has shown that the reasons lie in both biological and social changes that occur after puberty.

Dr. Mary Carskadon of Brown University is one researcher who discovered this biological link. By studying adolescents' melatonin levels, she showed that teenagers' bodies naturally tend to go to sleep and wake up later, called a delayed sleep phase preference (Johnson, 1998b).

While this new evidence deflects some of the blame for sleep deprivation from adolescents' personal choices and social pressures, those factors should not be disregarded. All too often, sleep simply "becomes a disposable commodity," says Caldwell (p.189). As students grapple for time between activities, jobs, and schoolwork, sleep suffers. Furthermore, Stanley Coren points out, many people unfortunately view "the person who sleeps in...as lazy while the person who goes without sleep is strong and to be admired" (p. 124).

What can be done to stop this sleep deprivation epidemic? One way to curb adolescent sleep deprivation is education. Parents and schools need to emphasize the importance of sleep and the damaging consequences of missing it. Also, a compelling new movement is gaining ground in the United States which advocates pushing back high school's starting time.

Adolescents' desire for a delayed sleep phase is inconsistent with the traditional 7:30 a.m. beginning to the school day. James Maas (1998) found that "30% [of high school students] fall asleep in class at least once a week" (p. 7). Contrary to popular belief, this tendency for students to nap at their desk cannot be attributed to boring teachers or laziness. Actually, explains Dr. William Dement of Stanford University, these circumstances simply "unmask any tendency to fall asleep that is present already" (n.pag.). Schooltime sleepiness, which causes decreased awareness and missed lessons, obviously hinders the educational process: the Carskadon and Wolfson survey found the average bedtime of D/F students to be nearly an hour later than that of A/B students.

Opponents of starting the high school day at 8:30-9:30 a.m. say the possible educational benefits are not worth the trouble. The primary criticism of a later high school day is its impact on after-school activities and jobs. Some ask how outdoor sports teams would fit in events before darkness. The only option might be excusing students early from class (CAREI, 1997). Opponents also note that hours students could work at part-time jobs would decrease (Kennedy, 1997).

Another argument contends that if students are sleep deprived because of a busy schedule, starting school later can do nothing to correct that. Whatever time is gained in extra morning sleep would be lost as students' job, homework, and socializing hours extended further into the night (G. Gritzon, personal communication, January 12, 1999).

Nowhere has the school start time debate been more active than Minnesota. In 1994 the Minnesota Medical Association urged all schools to adopt a later schedule (Lawton, 1995). The first to comply was Edina, which changed the beginning of first hour from 7:20 to 8:30 in 1996. Minneapolis and other school districts soon followed suit (Reiss, 1997).

These changes provide a large-scale case study to show if reality will follow the theorized effects. Many anticipated problems have indeed arisen. For instance, Earl Rainey, a student in Minneapolis, complains that the one hour and twenty-five minute later start time pushed his basketball practices to 7 or 8 p.m. "I wouldn't have time [in the evening] to do my homework. Then I'd have to get up early in the morning to do it, so I wouldn't get the extra hour of sleep" (as cited in Draper, n.pag.).

Edina has had similar problems, but overall the response has been overwhelmingly positive. A parent survey found 93% were pleased with the later start (CAREI). The most noticeable improvement has been in first period class. Before, "one-third to one-half of students might as well have had their heads on their desks," comments teacher Pacy Erck. Now "there's a personality to the first class. I feel the comprehension...is greater" (as cited in Johnson, 1998a, n.pag.). Plus, first period attendance rates are up. According to administrators, "the later start has had a positive

impact on the climate of the school" (CAREI, n.pag.).

To correct teenage sleep deprivation, the importance of sleep should be taught and, evidently, high school start times should be delayed. The fact is, for teenagers, Ben Franklin's aphorism "early to bed, early to rise, makes a man healthy, wealthy, and wise," may simply be unwise.

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SIDS: Why Did it Happen to Us?

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A young mother wakes up to an empty feeling and when she reaches her baby, she finds he is dead. Immediately she

calls 911, but the paramedics are unable to do anything. After a thorough autopsy, which is a legal requirement that must be performed when a child dies suddenly for no apparent reason, there is still no visible cause of death (Lingam, 65). The doctor states that the baby died from Sudden Infant Death Syndrome, or SIDS. Many mothers face this tragic phenomenon each year. This sudden death occurs in one out of every 800 apparently healthy children from the age of four weeks to one year, especially those babies between two to four months old (Lingam, 65). Ninety percent of all SIDS victims are less than six months of age (SIDS Alliance, 1).

SIDS, also known as cot death, occurs in babies of all races, socioeconomic groups, and religions (SIDS Alliance, 1). Statistics show that the SIDS risk in African Americans' and Native Americans' doubles that of Caucasians' (Laliberte, 84). Boys are also at a slightly greater risk than girls (Lingam, 65). Lower socioeconomic groups have more chance of their babies having SIDS also, but just because they are usually less able to properly care for an infant and make sure it has its necessary check-ups (Merck Research Lab., 2049). The risk for cot death also increases in multiple births, bottle-fed babies, premature babies, low-birth weight babies, and those who had difficulties breathing at the time of birth (Lingam, 65). Other increased risks include: infants who have suffered from severe apnea requiring resuscitation, in subsequent siblings of SIDS victims, and in infants born to mothers who smoked during pregnancy or around the baby after its birth (Merck Research Lab., 2049). However, cot death does not always occur in babies with these misfortunes.

Causes of sudden death infant syndrome are unknown, but there is still research going on to figure out why this unexplained death occurs. Many babies do not show any symptoms prior to their death; however, some infants have had a cold, a runny nose, a slightly high temperature, listlessness, drowsiness or even a small difficulty breathing (Lingam, 65). Cot death occurs many times in babies who sleep on their stomachs and are bundled in soft blankets and pillows, or sharing a bed with a parent (Laliberte, 82). This could be because SIDS causes something to interfere with their normal survival instinct, and they do not react to anything that interferes with breathing. Studies at Harvard reported that SIDS could result from an abnormality in a part of the brain known as the arcuate nucleus, which processes information about breathing and other vital functions. These defects could disrupt communication in the brain stem, preventing a baby from responding to a lack of oxygen or other potentially deadly problems during deep sleep (Laliberte, 82-84). Many times SIDS occurs in the fall and winter months when parents tend to overheat their babies. When the weather becomes colder, many parents put extra clothing on their baby and keep him in a warm room. Since the risk of SIDS increases when the baby's body temperature is excessively high, parents need to make sure they lie their babies on their back so that they can regulate their own temperature and prevent overheating better (Lingam, 65). A large number of babies that die of SIDS have a longer corrected QT

interval, a cardiac disorder which can produce fainting spells, seizures, and sudden death, than other infants. However, the SIDS victims had no family history of long QT syndrome. The inability to shorten the QT interval during increases in heart rate may be involved in SIDS. Sudden noise, exposure to cold, rapid eye movement, sleep apnea, and arousal are all possible reasons for increases in newborn heart rate (SIDS Research of Ore., 1). Another cause could be that mothers give their babies antibodies from their bloodstream in the womb. When the baby is born, these antibodies gradually disappear, and it takes several months for the babies to make their own antibodies. This causes antibodies in a baby's bloodstream to be at its lowest between the ages of two and four months, therefore making the baby most susceptible to infection during this period. A few doctors hypothesize that mild viral infections or toxins from bacterial infections may have a greater effect on the baby during this time of their life. An abnormality in the way the breathing passages work is sometimes triggered by a baby's allergic reaction of cow's milk protein. This may be the reason breast milk boosts the immune system causing the baby to be able to fight whatever causes SIDS. Another possible cause of cot death is apnea, the cessation of breathing. It is not uncommon for people to have periods of apnea lasting a few seconds, but they usually take a deep breath and everything is okay. However, in babies, a developmental defect of immaturity in the brain centre that controls breathing involuntarily may prevent the normal breathing pattern from being resumed (Lingam, 65).

As you might see SIDS is a very serious illness that unfortunately is very mysterious. Hopefully, researchers will soon find the cause of this sudden death and it can be prevented. Although only 1.5/1000 live births in the USA result in SIDS, parents need to take special precautions including: lying their baby on their back or side, keeping the temperature between 18 degrees Celsius and 20 degrees Celsius, not smoking around the baby, and not putting too much bedding down for the baby to sleep on (Merck Research Lab., 2048 and Lingam, 66).

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The Effects of Caffeine on the Sleep-Wake Cycles of Children and Adults

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Caffeine is the most widely consumed psychoactive substance, with worldwide caffeine consumption at about 120,000 tons annually. A methylxanthine, caffeine is found in a wide variety of items, primarily coffee and tea, but also soft drinks, chocolate, and cocoa. The average American child or adolescent consumes only about 43 milligrams of caffeine, compared to about 200 mg for American adults (Arbeit, 1988). Nonetheless, children and adolescents still ingest a large amount of caffeine, mostly from chocolate or soft drinks. Therefore, it is important to understand the effects of caffeine on health, and especially sleep, in children and adults. Most studies have shown that between children and adults, caffeine has similar effects on sleep, more alerting effects in children, but fewer other side effects in children. In discussing caffeine's effects, it is important to consider the entire sleep-wake cycle, as well as other side effects.

In almost all subjects, caffeine has a disruptive effect on sleep. Most studies indicate that when ingested in large doses (greater than about 250 milligrams or approximately three or four cups of coffee), caffeine shortens subjects' sleep duration and lowers their perceived sleep quality. One study showed that on subjective sleep questionnaires, 87% of patients ingesting caffeine reported that their sleep was shorter than usual, while only 43.5% of subjects who did not ingest caffeine reported that effect (Smith, 1993a). Another study found that sleep latency was almost three times longer in young adult males drinking four cups of coffee (or a four-cup caffeine equivalent) before bedtime than for subjects drinking a glass of warm water (Karacan, 1976). Subjects ingesting caffeine were also almost twice as likely to awaken in the middle of the night. The same study also showed, however, that one cup of coffee thirty minutes before bedtime has almost no effect on sleep.

Although infants' sleep appears to be more significantly affected by caffeine than that of adults, researchers have generally found that large doses of caffeine have the same negative effects on the sleep of children as on the sleep of adults (Hronsky, 1987). A survey of eleven, thirteen, and fifteen-year-olds showed that coffee had a significant effect on their perceived tiredness, but not as strong an effect as alcohol or cigarettes. In general, the effects of caffeine on any individual can vary greatly depending on certain factors, including metabolic rate and the individual's usual consumption of caffeine.

Caffeine increases the level of arousal during sleep, and it also generally improves alertness and performance during wakefulness. In one study, both 75 mg and 150 mg doses of caffeine sig-

nificantly improved scores on vigilance reaction tests after either eight hours or five hours in bed the preceding night (Rosenthal, 1991). Another study showed that subjects given 250 mg of caffeine had lower reaction times and fewer recall errors than subjects given placebos on each of three days of testing (Zwyghuizen-Doorenbos, 1990). Even though subjects were only given caffeine or placebos on the first two days, subjects who had taken caffeine those two days still had improved performance on the third day. Subjects ingesting caffeine are significantly more alert than subjects on placebo both in the day and at night (Smith, 1993b). Also, studies have shown that subjects who have ingested caffeine the previous night (and consequently, have slept poorly) perform similarly in the morning to subjects on placebo who have slept well.

Studies have shown that caffeine has even more marked effects on alertness in children than in adults. One study showed that children on high doses of caffeine were more active, had higher speech rates, made fewer errors in an attention test, and had shorter reaction times than children on placebo (Rapoport, 1981b). While the scores on these tests were not significantly different between adults on caffeine and adults on placebo, the differences between children on caffeine and those on placebo were very large. These results suggest that children and adolescents could potentially counteract the effects of sleep deprivation with caffeine, but they also risk disrupting sleep.

However, although children's performance is affected more by caffeine than that of adults, children complain of fewer subjective side effects. In higher doses, especially among low caffeine users, adults often complain of headaches, stomachaches, or nausea. Children seldom complain of these effects when given either low or high doses of caffeine (Rapoport, 1981b). Still, in many studies, children are often reported to feel "nervous or jittery" when taking high doses of caffeine. Children, teachers, and parents generally report that children who usually consume low amounts of caffeine report more side effects from large doses than children who are high consumers of caffeine (Rapoport, 1981a). Both children and adults who consume caffeine regularly can become dependent on the drug and often complain of headache, irritability, nervousness, restlessness, and lethargy while abstaining from caffeine.

Many important effects of caffeine on children and adolescents have yet to be studied thoroughly. For the most part, caffeine seems to have similar effects on the sleep-wake cycle of adults and children. Both children and adults become more tolerant of caffeine (and are consequently less affected by the drug) as their consumption increases. However, high consumption of caffeine also leads to caffeine dependence. Compared to children not ingesting caffeine, children ingesting large amounts of caffeine sleep less soundly and have longer sleep latencies, but also have enhanced alertness. While alertness is generally affected more by caffeine in children than in adults, children report fewer side effects. Nonetheless, low caffeine consumers (both children and

adults) are often negatively affected by large doses of caffeine. Although caffeine can counteract sleep deprivation, it also disrupts sleep and creates other negative side effects. Caffeine does improve alertness, but high doses are not recommended for children and adolescents because they may disrupt sleep or cause caffeine dependence.

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The Vicious Circle: Caffeine and Chronic Sleep Deprivation in Western Countries

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Does caffeine used to battle the effects of lost sleep actually contribute to a chronic sleep deprivation in the Western world? Evidence can be found to support the high level of caffeine consumption and the chronic sleep deprivation in Western countries. The effects of caffeine, while temporarily countering the effects of sleep deprivation, decrease sleep efficiency and may actually contribute to chronic sleep deprivation. This creates a vicious circle, wherein caffeine use leads to sleep deprivation, which leads to caffeine use, which leads to further sleep deprivation. As repeated caffeine use decreases the user's sensitivity to the effects of caffeine, increasing amounts of caffeine will be necessary to counter the effects of sleep deprivation.

There is a wealth of evidence to support the high level of caffeine consumption, not only in Western countries, but all over the world. Two major sources of caffeine are coffee and cocoa beans. In 1996-1997, 6,234,000,000 kilograms of green coffee, or the coffee fruit in which the beans are contained, was produced worldwide. Also in 1996-1997, 2,717,000,000 metric tons of cocoa beans were produced worldwide. (Paarlberg, 1999) As the level of a product's production generally mirrors the level of its consumption, these production statistics demonstrate the high level of caffeine consumption in the world today. Another statistic supporting this is that roughly a third of the world's population drinks coffee (*Encyclopedia Britannica, s.v., "Coffee,"* 15th Edition), a substance which is generally used for the effects of the caffeine contained therein. This is an indication of a high level of caffeine consumption as well.

The assumption that many people in Western countries are chronically sleep-deprived can also be supported. According to Professor Stanley Coren in his *Sleep Thieves: An Eye-Opening Exploration into the Science and Mysteries of Sleep*, studies show that the average North American or European adult gets an average of 7 hours and 20 minutes of sleep each night. However, in studies where subjects are permitted to asleap for whatever

length of time they wish, subjects tend to extend their sleep time. One such study resulted in an average sleep time of 10.3 hours, while the average sleep time of subjects in another was approximately 9 hours. Therefore, the average North American or European adult "may be getting 2 1/2 to 3 hours a night less sleep than our bodies and minds were designed to have" (Coren, 1996) and consequently, has a chronic sleep debt. (Coren, 1996)

The recognized effects of caffeine counter those of sleep deprivation. "Assessment of psychomotor performance, particularly tasks involving endurance, vigilance, and attention, shows that caffeine (100 to 400 milligrams) improves performance in such tasks." (Roehrs, 1995.) However, in many studies this effect is observed only in those subjects suffering from lack of sleep, whereas fully rested and alert subjects do not seem to derive measurable performance benefits from caffeine. This supports the theory that caffeine directly counters the reduction in performance level caused by sleep deprivation.

However, caffeine used during the day or in the evening, in order to counter the effects of sleep deprivation, has a negative effect on the length and quality of sleep. Caffeine, in doses of 100 to 400 milligrams, causes sleep to begin later, which, in a situation where a set period of time is allowed for sleep, would create a shorter sleep time. Once sleep has begun, caffeine reduces sleep efficiency and increases wakefulness and nighttime awakenings. Also, this dosage increases the time spent in Stage 1 sleep, and decreases the time spent in Stages 3 and 4 sleep. (Roehrs, 1995) Since Stage 1 is a light, generally transitional stage, whereas Stages 3 and 4 are deep stages of sleep, (Keenan, Herman, and Carskadon, 1995) an increase in the former and a decrease in the latter would result in less restorative sleep, contributing to sleep deprivation.

Another effect of caffeine which may contribute to chronic sleep deprivation is a "systematic dose-related increase in the average latency to sleep onset." (Roehrs, 1995) As the dosage of caffeine increases, the subject takes longer and longer to fall asleep.

Since, as already observed, in a situation where a set amount of time is allowed for sleep, a later sleep onset decreases total sleep time, the greater the dosage, the lesser the sleep time. If a person is running a chronic sleep debt, this will contribute to it, which may prompt the use of more caffeine in order to offset the effects of sleep deprivation. Since repeated caffeine use decreases sensitivity to the "alerting effects" of caffeine (Roehrs, 1995), more caffeine will be necessary to counter the effects of sleep deprivation, leading to a later sleep onset, which will create still more sleep deprivation. This evidence leads to the conclusion that the use of caffeine to offset the effects of sleep deprivation creates a vicious circle. The effects of caffeine reduce sleep efficiency, adding to sleep deprivation, which causes further caffeine use, decreasing the user's sensitivity to the effects of caffeine and forcing the use of greater and greater amount of caffeine to counter sleep deprivation's effects. People in Western countries con-

sume the caffeine for its immediate effects, without realizing that it actually causes the tiredness which they consume it to abate. However, even if given this knowledge, one doubts that the average American would be persuaded to give up his or her cup of coffee in the morning!

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N.B.; Many of the scientific studies and data which are referred to in the essay were originally published in a scientific journal or magazine and cited in the sources used; however, due to a lack of access to the original sources, many of the citations within the essay refer to general sources which themselves cite the individual scientific study in its original published form.

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SRS Supports Trainee Workshop at Neuroscience Satellite Meeting

The Sleep Research Society provided a grant to Dr. Allan Pack, University of Pennsylvania, to support a trainee workshop in conjunction with a satellite meeting to the recent Society for Neuroscience meeting in Miami, Florida. The satellite meeting was sponsored by the American Physiological Society and was held from October 19-22 in Fort Lauderdale, FL. The goal of the meeting was to discuss how the sleep and circadian systems might interact. The meeting allowed leading investigators in sleep and circadian rhythm research to describe their latest findings and then to discuss how the systems might interact. The consequences of, and evidence for, the interaction were also explored. A breaking news session on genes for narcolepsy was included.

The meeting had the following speakers and topics:

Evidence for Interaction Between Sleep and Circadian Systems

Chair: Robert Moore, M.D., Ph.D. (University of Pittsburgh)

Nature of Interaction in Humans

Charles Czeisler, M.D., Ph.D. (Harvard University)

Species Differences in Nature of Interaction

Irene Tobler, Ph.D. (University of Zurich)

Nature of Interaction in Rodents and Primates

Dale Edgar, Ph.D. (Stanford University)

Interactions Between Substates of Sleep

Craig Heller, Ph.D. (Stanford University)

Molecular Basis of Circadian Clock

Chair: Fred Turek, Ph.D. (Northwestern University)

Molecular Basis of the Circadian Clock

Amita Sehgal, Ph.D. (University of Pennsylvania)

Functioning of Circadian Clock in Mice

Larry Pinto, Ph.D. (Northwestern University)

Mammalian Per Genes

Steven Reppert, M.D. (Massachusetts General Hospital)

Molecular Mechanisms of Resetting

Martha Gillette, Ph.D. (University of Illinois)

Mechanisms Controlling Sleep: Networks and Systems

Chair: Adrian Morrison, D.V.M., Ph.D. (University of Pennsylvania)

Brainstem Mechanisms of REM Sleep

Robert McCarley, M.D. (Harvard University)

Forebrain Thermoregulatory Systems and Sleep Control

Ronald Szymusiak, Ph.D. (UCLA)

Role of Amygdala in Sleep Control

Larry Sanford, Ph.D. (University of Pennsylvania)

Thursday, October 21

Sleep Promoting Factors-Part One

Chair: Alexander Borbely, M.D. (University of Zurich)

Cytokines and Sleep Control

James Krueger, Ph.D. (Washington State University)

Prostaglandins and Sleep Regulation

Osamu Hayaishi, M.D., Ph.D. (Osaka, Japan)

Adenosine and Sleep Promotion

Robert Greene, M.D., Ph.D. (Harvard University)

Sleep Promoting Factors-Part Two

Chair: Alexander Borbely, M.D. (University of Zurich)

Multiple Pathways for Sleep Homeostasis

Allan Pack, M.D., Ph.D. (University of Pennsylvania)

Melatonin: Molecular Mechanisms of Action

David R. Weaver, Ph.D. (Massachusetts General Hospital)

Could Interaction be Neurohormonal or Neurochemical?

Chair: Irene Tobler, Ph.D. (University of Zurich)

Diurnal Variations in Vigilance: Neuroendocrine and Metabolic Concomitants

Eve van Cauter, Ph.D. (University of Chicago)

Evidence from Transplant Studies

Rae Silver, Ph.D. (Columbia University)

Could Interaction be Neuroanatomical?

Chair: Gene Block, Ph.D. (University of Virginia)

Neuroanatomical Connections of SCN

Robert Moore, M.D., Ph.D. (University of Pittsburgh)

Brainstem Circuitry for Sleep Control: Interactions with SCN

Gary Aston-Jones, Ph.D. (University of Pennsylvania)

Hypothalamic Connections

Clifford Saper, M.D., Ph.D. (Harvard University)

Friday, October 22

Consequences of Interaction-Quantitative Aspects

Chair: Michael Menaker, Ph.D. (University of Virginia)

Models and Concepts of Sleep Regulation

Alexander Borbely, M.D. (University of Zurich)

Circadian and Homeostatic Components of Sleep Consolidation, REM Sleep and the Electroencephalogram

Derk-Jan Dijk, Ph.D. (Brigham and Women's Hospital)

Consequences for Neurobehavioral Functions

David Dinges, Ph.D. (University of Pennsylvania)

Consequences of the Interaction Between Circadian and Sleep Systems: Other Systems

Chair: David Dinges (University of Pennsylvania) and Mary Carskadon (Brown University)

Consequences for Adolescents

Mary Carskadon, Ph.D. (Brown University)

Consequences for Military Operations

Gregory Belenky, M.D. (Walter Reed Army Institute of Research)

Sleep/Circadian Aspects of Respiratory Control

Steven Shea, Ph.D. (Harvard University)

To Sleep, Perchance to Wake. The Relationship Between Sleep and Cardiovascular Death and Disease

Virend Somers, M.D., D.Phil. (Mayo Clinic)

Consequences of Sleep Deprivation on Neurohormonal and Immune Systems

Janet Mullington, Ph.D. (Harvard University)

The meeting was attended by 173 individuals. The Sleep Research Society supported the travel of 30 trainees who had applied to the SRS for awards. The successful applicants were: J. Todd Arnedt, Elda Arrigoni, Alvhild Alette Bjorkum, Michelle Brosemer, Melissa Burnham, Orfeu Buxton, Mairav Cohen-Zion, Deirdre Conroy, Michael Decker, Scott Doran, David Ehrlich, Helene Gaudreau, Philip Gehrman, Laurel Graves, Claude Gronfier, Hiroshi Kadotani, Ron Leder, Rachel Leproult, Wah-Ping Luk, Georgios Mitru, Nicolette Meunter, Luz Navarro, Ana Ribeiro, Paul Shaw, Teresa Steininger, Elizabeth Teodecki, Ramesh Vijay, Christopher Winter, Kenneth Wright, Rochelle Zozula

The trainees attended all of the scientific sessions. Following the satellite meeting a trainee workshop was held for one day. Trainees were asked to determine the next critical question based on what they heard at the meeting. They then designed studies to address this question. Trainees presented their ideas to the group of faculty and trainees. Social events included beach volleyball, buffet dinner, etc. provided by the Center for Sleep and Respiratory Neurobiology, University of Pennsylvania. Faculty who participated in the trainee workshop included: Gary Aston-Jones, Alexander Borbely, Mary Carskadon, Lynn Churchill, Dale Edgar, Martha Gillette, Robert Greene, Adrian Morrison, Janet Mullington, Allan Pack, Larry Sanford, Rae Silver, Virend Somers, Ron Szymusiak, and Irene Tobler.

The trainee workshop concluded with transportation organized to Miami and the Society for Neuroscience. The Sleep Research Society hopes that others will apply for grants to develop trainee workshops. For information concerning deadlines and procedures for applying for Trainee Workshops, please contact Dr. Dale Edgar.

SRS Response to the Center for Scientific Review Phase 1 Draft Report of the Panel on Scientific Boundaries for Review

On behalf of the members of the Sleep Research Society (SRS), we are writing to comment on the Phase I Report of the Panel on Scientific Boundaries for Review. We read the report with great interest and feel it provides an excellent template for the future of the NIH review process.

1. The goals of the program resonate with the SRS scientific standards and our sense of fair play. We encourage CSR to continue to explain the review process and to monitor it vigilantly.

2. The SRS is also quite pleased to read the guiding principles that were used by the Panel in formulating the proposed IRG system. In particular, our members are familiar with the process of research review related to a given disease taking occurring the context of basic research. The proposed IRGs appear adequately to foster this mechanism in general.

The structure of the new IRGs and the specific proposed entities likely will succeed in providing a thorough and fair review of our science, while maintaining adequate flexibility to account for rapid shifts in methods, concepts, and theoretical outlooks. The rationales put forth for the new IRG system seem cogent and almost inevitable, given the current needs of biomedical research. SRS applauds the Panel's efforts to shape the NIH review process in a way that bends to the needs of the next millennium but does not break this powerfully effective system of peer review.

Many members of the SRS over the last 40 years have benefited from NIH funding, have served and are serving on or chairing review committees and institute advisory panels. As a scientific society, we are enthusiastically supportive of the NIH. As with many other fields, our members tackle our basic scientific and clinical research issues in sleep, sleep disorders, and biological

rhythms with a variety of methods and research techniques, though often with a common heritage of ideas and constructs. Hence, review of our science benefits if reviewers share this background and expertise.

The present cluster of former NIMH and ADAMHA review committees has apparently been subsumed under the proposed IRG system and includes two panels with an explicit emphasis on sleep and biological rhythms - 19. Integrative, Functional, and Cognitive Neuroscience and 20. Brain Disorders and Clinical Neuroscience. These committees seem to have worked well for reviews for our members, yet we note that many of our members' research projects may not be best placed solely in the proposed committees. Thus, for example, research on the pathophysiology of sleep and breathing diseases such as OSA may best be reviewed in the context of IRG 17, Pulmonary Sciences. Other areas of research in sleep biorhythms and sleep disorders are more logically reviewed by IRGs with a focus on health behavior, such as IRG 6, Health of the Population; IRG 7, Risk, Prevention, and Health Behavior; and IRG 8, Behavioral and Biobehavioral Processes. Perhaps the descriptions of these IRGs might also include mention of sleep, sleep disorders, and biological rhythms.

These comments are offered by the SRS in an attempt to broaden the Panel's understanding of sleep, biological rhythms, and clinical sleep research. SRS members are well trained in disciplines that support their research, whether that training is in basic neuroscience, pulmonary physiology, molecular biology, behavioral medicine, psychology, or other disciplinary backgrounds. Thus, we hope that the SRS members and CSR can continue a course that benefits both in providing adequate and fair reviews that maximize the scientific benefit to the community.