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14. ABSTRACT

This DURIP grant made possible major technological advances at the three sites of the AFOSR PRET Center (University of Pennsylvania, Harvard University and Stanford University), substantially improving the Center's capability to study the neurobehavioral and neurobiological deficits associated with sleep deprivation and jet lag, and the development of countermeasures, in the context of simulated sustained operations. At Stanford University, a state-of-the-art pre-clinical sleep-wake bioassay technology (SCORE-2000) was developed and employed for the clinically predictive testing of countermeasures in animals. At the University of Pennsylvania and at Harvard University, integrated systems for the on-line measurement of a range of physiological and neurobehavioral variables in humans were purchased, installed, tested and operationalized. Thus, from pre-clinical animal studies to application in human laboratory studies, the DURIP grant considerably streamlined and expanded the PRET Center's efforts to identify, evaluate and transition countermeasures to deficits associated with sleep deprivation and jet lag.

15. SUBJECT TERMS
Research grant is issued under the Federal Demonstration Partnership (FDP) III.

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DURIP: Center on Countermeasures Prevention of Human Performance Failure From Biological Vulnerability: Achieving Optimal Capability

Final Report: April 1, 1999 to September 30, 2000

Grant Number: F49620-99-1-0170

Title: Center for Countermeasures Prevention of Human Performance Failure From Biological Vulnerability: Achieving Optimal Capability

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DURIP Final Report
University of Pennsylvania Component
Principal Investigator: David F. Dinges, Ph.D.

University of Pennsylvania executive summary report:

The equipment requested in the proposal was purchased and incorporated into the basic scientific research of the AFOSR PRET Center. This research involves the development of technologies to overcome the neurobehavioral and neurobiological deficits associated with sleep deprivation and jet lag. In addition, this equipment facilitated the research and related science education of a multi-university, multi-disciplinary research initiative (MURI).

Specifically, this equipment grant facilitated the integration of new ambulatory and on-line technology for integrated monitoring of human physiology (EEG, EOG, EMG, ECG) and neurobehavioral alertness (vigilance performance, eyelid closures) for early indentification and prevention of performance failures due to sleep loss and circadian phase during simulated sustained operations.

The purchased polysomnographical units were tested extensively in laboratory protocols, and based on our experiences some modifications were made by the manufacturer to further optimize data quality. Together with the core body temperature recorders and the actigraphs, for which only a limited amount testing was found to be needed, the polysomnographical units currently provide a fully operational complement of human physiological measures, which are being intregrated into the recently renewed AFOSR PRET Center research.

All computer software and hardware to handle the various recordings and data analyses are in place. While the PERCLOS monitors for eyelid closures are undergoing calibration at this time, they are also being integrated into the recently renewed AFOSR PRET Center research, utilizing the purchased computer hardware to full capacity. Finally, a computer server was installed to handle the increased amount of data gathered in our simulated sustained operations research.

In conclusion, this DURIP equipment grant has substantially improved and refined our measurements of an increased range of human physiological and neurobehavioral variables in the context of sleep loss and circadian rhythmicity during simulated sustained operations - from recording to data management, reduction and analysis.

Publications:

Hughes, RJ, Vandongen, H, Dinges, D, Rogers, N, Wright, KP Jr., Edgar, DF, Czeisler, CA. Modafinil improves alertness and performance during simulated night work. Sleep; In press.

Major Purchases under this agreement

Item	Quantity
Vitaport polysomnographical units (TEMEC)	6
Mini-Logger core body temperature recorders (Mini-Mitter)	6
High-end personal computers for neurobehavioral alertness recording	6
C.D. rewritable recorders for data archiving	6
PERCLOS eyelid closure monitors	5
Computer server (Windows NT)	1
High-end laptop computers for on-site polysomnographical unit programming	4
Actiwatch-L actigraphs (Cambridge Neurotechnology)	6

DURIP Progress Report
Harvard Medical School Component
Principal Investigator: Charles A. Czeisler, Ph.D., M.D.

Harvard Medical School executive summary report:

In the period covering 9/99 -9/00, we received and implemented the use of equipment for the measurement of wake-sleep actigraphy and light exposure recording, minute-by-minute samples of core-body temperature; neurobehavioral performance testing, polysomnographic and waking EEG recording equipment.

The equipment acquired under the DURIP provided the state-of-the-art infrastructure that allowed us to obtain research funds for a pilot grant assessing the novel wake-promoting drug modafinil in a simulated jet-lag night-shift protocol. This pilot study provided important preliminary work for our currently funded AFOSR PRET investigation entitled "Homeostatic & Circadian Regulation of Wakefulness During Jet Lag and Sleep Deprivation: Effect of Wake-Promoting Countermeasures". The equipment purchased is also currently used in our AFOSR PRET study.

Data collected with this equipment will be incorporated into a model of alertness and performance currently being developed to counteract fatigue associated with Air Force missions. The model is being developed as part of the AFOSR Partnership for Research Excellence and Transition Program (PRET), Center on Countermeasures for Jet Lag and Sleep Deprivation organized at the University of Pennsylvania.

Major Purchases under this agreement

Item	Quantity
Computer equipment and system software for neurobehavioral performance assessment and storage of performance data	
Portable EEG data acquisition systems for assessment of waking vigilance	10
Wrist Actiwatch-L recorders for monitoring sleep-wake activity and light exposure	16
Telemetry monitors for assessment of circadian core body temperature	6

There are no budgetary costs for personnel.

Publications:

Hughes, RJ, Vandongen, H, Dinges, D, Rogers, N, Wright, KP Jr., Edgar, DF, Czeisler, CA. Modafinil improves alertness and performance during simulated night work. Sleep; In press. Additional publications are in preparation.

Participation/presentations:

Czeisler, CA. Recent Treatments of Performance-Impairing Sleepiness Associated with Shift Work and Acute Sleep Loss. Association for Professional Sleep Societies, Las Vegas, June 2000.

DURIP Final Report
Stanford University Component
Stanford Principal Investigator: Dale M. Edgar, Ph.D.

Stanford University executive summary report:

Overview:
The DURIP has made possible the creation of SCORE-2000™, the most advanced and clinically predictive pre-clinical sleep-wake bioassay technology in existence. SCORE-2000™ is a combination of custom software and "off-the-shelf" hardware that performs real-time sleep-wake, body temperature and locomotor activity assessments (wheel running, non-specific locomotor activity, drinking or feeding, and additional digital data variables) simultaneously. What set SCORE-2000™ apart from previous SCORE™ Technologies is the marriage of the sophisticated software and highly secure internet tunneling protocols that literally allow remote assessment, command and control of SCORE-2000 data collection systems from anywhere in the world via the internet. This technology is analogous in concept to the new remote field patient monitoring technologies developed by the DOD except that the Internet serves as the communications backbone. SCORE-2000™ is sufficiently advances that it has been licensed as the founding technology for a new start-up sleep-wake biotechnolgy & genomics company (see below).

Technology Transition:
This DURIP procurement together with support from the AFOSR-PRET, produced the SCORE-2000™ Sleep-Wake Bioassay Technology. Together with the SCORE Sleep-Wake Pharmacology Database, this comprises the most advanced and comprehensive tool for pre-clinical sleep-wake pharmacology in the world. Recognizing this, and in the spirit of recommendations made by our AFOSR-PRET Advisory Board, a new company was formed called "Hypnion, Inc." Hypnion is the first Biotechnolgy & Genomics company exclusively dedicated to the problems of sleep-wake disorders. Hypnion, Inc. has licensed SCORE-2000™ and the SCORE™ Sleep-Wake Pharmacology Database as the core technology of the company and will us it in efforts to discover better sleep-wake therapeutics and novel drug targets through modern genetics and functional genomics approaches. Hypnion, Inc. is exquisitely well suited to coordinate with DOD, large pharmaceutical companies, and academic institutions to make further rapid transitions in drug development.

The formation of Hypnion, Inc. and the licensing of the SCORE-2000 technology to Hypnion constitutes a bona fide transition of technology under this DURIP.

Specifications:
The new SCORE-2000™ technology operates under a hybrid computer platform involving Linux-based SCORE-2000™ data collection nodes (DELL Poweredge 1300 micro-servers), a single SUN Enterprise-450 data storage server, and multiple Windows-based SCORE-2000™ remote access workstations (Dell XPS-T600 and IBM 600E) and data analyses platforms (Dell Pecision 410 and 420 workstations). Together these computers and supporting hardware finction as a SCORE-2000™ network allowing cross-platform evaluation, analyses, and sharing of data for team application of analyses routines and high performance data analyses throughput.

Key New Features of SCORE-2000™ include:
- Real-time EEG, EMG and Scoring Template Display and paramater control via the Internet
- Capacity to monitor 16 animals per SCORE-2000™ node (up to 96 animals simultaneously)

- 400Hz EEG and EMG sampling rates (4x better than original SCORE™)
- Up to 16 Bit analog to digital resolution
- Real-time digital EEG filtering
- 5 digital detection channels with simultaneous Boolean detect and CPM
- RSA secured Internet tunneling protocols
- Multilayer authentication
- Triple layer real-time data redundancy (Raid-1 at nodes, Raid 5+0 at server)
- SCORE-2000 system sub-set security (limits user access to a subset of SCORE Resources)
- Compatible with multi-algorithmic consensus scoring processes (AI compatible)
- Real-time EEG artifact detection
- Real-time system failure notification system (Email, pager, etc)

Major Purchases under this agreement

SCORE-2000 Sleep-Wake Bioassay System, including custom software and hardware components as follows:

Vendor	Item	Quantity
Astromed Grass	Model 12-32-23S	1
Stanford Software Systems	SCORE-2000 Linux/Win2K Software	1
Data Translation	DT3016 A/D	7
Data Translation	DT740 Terminal Panel	6
Data Translation	EP309 analog cable	6
Data Translation	DT301 A/D	8
IBM	Model 600E Notebook	1
IBM	2nd Battery	1
IBM	64K RAM	1
HP	LaserJet 5000N C4111A	1
Sun Microsystems	Ultra450 Server	1
Dell Computers	410 Workstations 2xCPU	3
Dell Computers	Poweredge 1300 Linux	6
Dell Computers	420 Workstations 2xCPU@800MHz	1
Dell Computers	XPS-T600 Win98	4
APC	APC SU2200NET	1
APC	APC Smart UPS SU1000NET	8
Crist Instruments	TBC-9 Commutators	30
CDW	Sony PCBacker 10000e	1
Sun Microsystems	Internal 18.2 GB HDD for E450	2
Newark Electronics	Belden Wire 500' 37lead & 100' 9 lead	1

Future Applications

In addition to the licensed use by Hypnion, Inc. (mentioned above), SCORE-2000™ will be used in academic settings to enhance basic research efforts sponsored both by DOD and PHS. The SCORE-2000™ system will not only revolutionize the efficiency and accuracy of the SCORE Sleep-Wake Bioassay process, but will make possible further preclinical developments based on important recent findings. Whereas out AFOSR sponsored research has previously focused on differentiating the advantages and disadvantages of methamphetamine, caffeine and

modafinil as a therapeutic countermeasures for impaired alertness, new research made possible by this equipment grant will allow us to investigate the therapeutic utility of a much wider range of new and atypical wake-promoting therapeutics. For example, our research partners at Gliatech, Inc. would like us to continue to assess a series of novel H3 histaminergic antagonist medications with wake-promoting actions. These compounds are particularly exciting because they not only act on well documented natural histaminergic wake-promoting mechanisms in the brain, but also may enhance cognitive performance. We believe this new-generation series of wake promoting therapeutics can be targeted for mission critical applications where sleepiness and impaired cognitive performance due to sustained operations could lead to catastrophic loss. Gliatech, Inc. also anticipates major applications for this series of medications in Alzheimer's disease which is characterized by cognitive deterioration and severe sleep disorders.

Additional preclinical discovery made possible by the new SCORE-2000™technolgy includes studies of Pemoline (Cylert®) and a family of selective dopamine reuptake blockers that shows great promise for sustaining wakefulness without producing incremental or synergistic increases in compensatory sleep drive (a serious problem with currently available psychostimulants). We have recently found that Pemoline, a medication often used for attention deficit hyperactivity disorder (ADHD), and a family of selective dopamine reuptake blockers (DARBs) can produce sustained wakefulness that is completely uncoupled from the mechanisms that normally produce sleepiness and compensatory hypersomnolence associated with sleep deprivation. Our findings suggest that we can indeed tap into the most fundamental mechanisms of sleep regulation and pharmacologically control the physiological processes responsible for sleepiness. Before this remarkable finding can be extrapolated for use in humans, however, studies of drug interaction with pre-existing sleep loss, efficacy measures as a function of time of day are vitally needed, and animal modeling of drug effect and side effects during pharmacologically enhanced sustained operations are needed. Similar studies are also needed for numerous promising new candidate compounds we have identified in the selective dopamine reuptake blocker class. Based on our preliminary data, compounds including GBR12909, GBR12783, 4'4"-difluoro-3α(diphenylmethoxy) tropane, and amineptine each hold promise as novel "somnolytic" wake-promoting therapeutics. As noted for pemoline, however, several studies designed to: i.) validate the therapeutic efficacy of these drugs in sleep-loss and jet-lag scenarios, and ii.) assess novel drug medication interaction with commonly used over-the-counter and food stimulants (e.g., caffeine and theophylline) will be needed before these compounds can be safely advanced for human clinical trials.

Finally, it must be mentioned that, due to the very high data throughput of the new SCORE-2000 system, it will be possible to begin assessment of drug interaction at the preclinical level and assess the predictive utility of such interaction in humans. This is a critical area in drug development and a growing liability concern for industry. Based on preliminary evidence, we believe the SCORE-2000 technology holds promise for predicting undesirable drug interaction on sleep-wakefulness at the pre-clinical stage of drug development. This information will then advise the pharmaceutical industry prior to the costly efforts associated with clinical trials.

Because the need for safe and effective wake-promoting therapeutics is go great, the SCORE-2000™ Sleep-Wake Bioassay System is virtually certain to advance our preclinical discovery over the next decade, leading to the development of novel somnolytic medications. Indeed, these medications could revolutionize sleep disorders medicine and we currently know it.

Patents

There are no patents associated with SCORE-2000™ and Stanford University has declined interest in such an effort citing anticipated difficulty with patent enforcement. The software component of the technology was procured as a license agreement with Stanford Software Systems (a company that is not affiliated with Stanford University). Under this agreement, Stanford University purchased an Exclusive license to use SCORE-2000™, however the copyright was vested in Stanford Software Systems under terms of the Purchase and Sale agreement. Mr. Rand Wheatland dba Stanford Software Systems transferred the SCORE-2000 copyright to Dr. Dale Edgar, who in turn issued unrestricted sublicense authority to Stanford University.