

MIND body Connections

A Publication of the **COUSINS CENTER FOR PSYCHONEUROIMMUNOLOGY** AT THE **UCLA SEMEL INSTITUTE**

Cellular Health Can Turn On a Good Night's Sleep

"O sleep! O gentle sleep!

*Nature's soft nurse, how have I frighted thee,
That thou no more wilt weigh mine eyelids down
And steep my senses in forgetfulness?"*

*William Shakespeare,
"King Henry IV – Part II"*

Insomniacs have long commiserated with The Bard's ruminations on the pain of sleepless nights. Now UCLA neuroscientists are discovering the biological underpinnings for the metaphor of sleep as healer and protector.

Researchers at the UCLA Semel Institute for Neuroscience and Human Behavior are the first to show how sleep loss can prompt the immune system to turn against healthy tissue and organs.

Reporting last summer in the peer-reviewed journal *Archives of Internal Medicine*, the research team finds that tossing and turning for even a single night can trigger cellular and genetic processes that produce tissue-damaging inflammation.

The findings suggest a good night's sleep can ease the risk of both heart disease and autoimmune disorders such

as rheumatoid arthritis.

"Physical and psychological stress brought on in part by grinding work, school and social schedules is keeping millions of Americans up at night," said Dr. Michael Irwin, lead author and director of the Cousins Center for Psychoneuroimmunology at the Semel Institute. "America's sleep habits are simply not healthy. Our findings suggest even modest sleep loss may play a role in common disorders that affect sweeping segments of the population."

About one-third of the people in the United States have trouble getting a good night's sleep. The problem is more prevalent among people with chronic inflammatory disorders, including heart disease. In addition, studies looking at incidence and prevalence of disease link poor sleep with risk of chronic disorders in some people.

Inflammation, with its accompanying redness and swelling, occurs when the immune system floods a diseased or damaged portion of the body with

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DIRECTOR'S MESSAGE

Living a Legacy

During my five years as Director of the Cousins Center for Psychoneuroimmunology, I have been rewarded by the hallmarks of innovation, collaboration and forward thinking of the Semel Institute and the UCLA campus. The Center has superb faculty, some of the brightest students and trainees, and an internationally recognized program of research and education.



Irwin

Dedicated to carrying forward the vision of founder Norman Cousins, we emphasize the need to humanize medicine by encouraging patient engagement of emotional strength towards healing. If the brain plays an active role in

the healing process, might it be consciously directed for that purpose? What would the implications of such findings be on the treatment of serious illness?

The over-arching objective of the Cousins Center for PNI is to develop an understanding of the psychological and biological factors in disease, and how the resiliency of the human body can be aided by positive behaviors, attitudes, and emotions. Our goal is to prepare healthcare professionals to deliver effective treatments that focus on the individual as a whole, so that patients fully employ their intellectual and emotional resources in partnership with their physicians to facilitate recovery from illness. •

— Michael Irwin, M.D.

Brain Imaging Captures Pain of Social Rejection

Hey! Yo! Throw the ball to meeeeeee!” It’s a plea for inclusion heard floating on the breeze above hot asphalt playgrounds, weed-strewn vacant lots and neatly trimmed lawns across America. When the ball doesn’t come with regularity, it can hurt every bit as badly as a skinned knee or twisted ankle.

And the pain of rejection isn’t confined to kids’ games. Relationships involving friends, family and careers all hold their share of pain for adults. No one likes to feel left out.

Naomi Eisenberger, a National Institute of Mental Health postdoctoral fellow in psychoneuroimmunology at the UCLA Cousins Center, is using functional neuroimaging and a computerized ball-tossing game, called “Cyberball,” to investigate why social rejection hurts.

“We have learned that the pain of social rejection relies on many of the same brain structures that are involved in physical pain processing,” said Eisenberger, who will become an assistant professor of psychology at UCLA in July 2007. “These findings highlight the importance of social relationships for well-being. To the extent that social connection is important for survival, feeling ‘hurt’ by social rejection may be an adaptive way to prevent future social separation.”

And now Eisenberger and her colleagues are embarking on an examination of how activation of the immune system affects the brain’s response to social rejection. The study is the first to investigate the effect of systemic inflammation on the brain’s response to social and emotional processes, which may increase the risk of depression.

“These findings may have impli-

cations for understanding the role of inflammatory mechanisms in depression and have the potential to guide the development of new treatments for this disorder,” she said.

Eisenberger’s research requires the powerful functional magnetic resonance imaging (fMRI) equipment of the Ahmanson-Lovelace Brain Mapping Center at UCLA’s Jane and Terry Semel Institute for Neuroscience and Human Behavior.

Research subjects are invited to engage in a ball-toss video game

projected on special goggles while undergoing fMRI. The imaging technique takes advantage of the magnetic properties of blood to measure brain activity as a function of blood flow — the greater the flow, the greater the activity.

While each subject believes the game of virtual catch involves two additional participants, “Cyberball” actually pits the subject against a computer program. The first game involves an equitable exchange of the ball,

but the second degenerates into a frustrating game of “keep away,” with the subject left out. So no one leaves distressed, each subject is advised of the “fix” after reporting on how they feel about their gaming experience.

Eisenberger’s initial study found that the brain’s dorsal anterior cingulate cortex (dACC), typically associated with physical pain distress, plays a role in the feelings associated with social rejection or social loss. Higher levels of self-reported stress correlated with greater activity in the dACC.



Naomi Eisenberger uses brain imaging to investigate why social rejection hurts.

Photos: Reed Hutchinson

“We have learned that the pain of social rejection relies on many of the same brain structures that are involved in physical pain processing.”

In a separate exploratory study, she also found that subjects with higher proinflammatory cytokine levels reported more distress and showed more dACC activity during social rejection. The body produces cytokines when attacked by infection, virus or other foreign agent. Cytokines help the body fend off the attack by causing disease-fighting inflammation, with accompanying fever, fatigue and other sickness behaviors that prompt social withdrawal.

In her upcoming study, healthy subjects will randomly receive endotoxin, which will increase proinflammatory cytokine activity, or a placebo before undergoing fMRI while facing rejection during the digital ball-tossing game.

Eisenberger hypothesizes that individuals exposed to the endotoxin will report more social distress and depression following rejection and will show more dACC reactivity during rejection.

The research is funded by NARSAD and the Dana Foundation. •



Behavior – A Sixth Vital Sign in Cancer Patients

Behavior is emerging as a “sixth vital sign” for gauging the health and well-being of cancer patients and survivors.

A growing body of research literature is uncovering the complex, multi-layered link between behavior and cancer progression and recovery.

Researchers affiliated with the Cousins Center for Psychoneuroimmunology and Jonsson Comprehensive Cancer Center at UCLA are among those at the forefront of understanding how cancer and its treatments influence behavior, and how behavior influences the disease.

“Depression, fatigue, sleep disturbances and cognitive dysfunction brought on by complications of cancer and the toxicity of some treatments can plague cancer patients from diagnosis through recovery and beyond,” reports Dr. Michael Irwin, UCLA professor of psychiatry and biobehavioral sciences.

“Biobehavioral assessment of the causes and impact of these symptoms is yielding a wealth of new strategies for combating the progression of some cancers and for improving the quality of life of the more than 10 million cancer survivors in the United States,” Irwin said.

Peer support for survivors

Persistent, debilitating fatigue is a common complaint among cancer survivors. Annette L. Stanton, UCLA professor of psychology and of psychiatry and biobehavioral sciences, and colleagues recently conducted a study of biobehavioral influences on cancer patient fatigue and disease-related distress during the critical transition from patient to survivor, also called re-entry.

Reporting in the September 2005 *Journal of Clinical Oncology*, Stanton’s team found that a peer-modeling videotape developed for the project significantly accelerated recovery of energy during the re-entry phase, particularly among women who feel less prepared for re-entry. The video is now available through the National Cancer

Information Service and its impact will be examined further in future research.

“I am really encouraged that our intervention actually has immediate clinical applicability, and we’re working to strengthen that intervention,” said Stanton.

Her current work also includes an examination of behavior and neuroendocrine function in women with metastatic breast cancer and a study of psychological well-being and immune function in women who have been tested for the breast cancer gene.

Stress and tumor growth

Steve Cole, UCLA professor of medicine in the Division of Hematology/Oncology, specializes in development of computer algorithms used to pinpoint signaling pathways that affect specific cellular behavior. “We are currently applying these techniques to understanding how psychological factors and the social environment affect the biology of cancer cells,” he said.

Cole co-authored a study published in the August 2006 edition of *Nature Medicine* that examined the impact of stress on mice implanted with ovarian cancer cells. In addition to finding that tumors in mice under stress grew and spread faster, the study pinpointed a specific receptor on the surface of a cancer cell that allowed a stress hormone to accelerate the growth of blood vessels that support the tumor and help it to spread.

Immunity factors

Reporting in the May 1, 2006, edition of *Clinical Cancer Research*, Irwin reported that breast-cancer survivors with persistent fatigue had increased levels of interleukin-6, a protein produced by immune cells to increase disease-fighting inflammatory reactions.

“Our findings not only help explain their fatigue but indicate potential targets for dealing with the debilitating fatigue experienced by so many cancer survivors,” he said.

Irwin also recently received a grant from the National Cancer Institute to examine the impact of tai chi on chronic insomnia and immune mechanisms in breast cancer survivors.

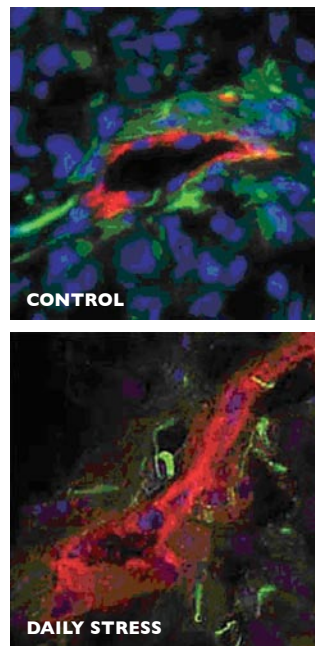
Yoga therapy

Julienne Bower, assistant professor of psychology and psychiatry and biobehavioral sciences at UCLA, recently received a National Center for Complementary and Alternative Medicine grant to conduct the first randomized, controlled clinical trial of yoga for fatigue among breast cancer survivors.

“We are interested in yoga because we have compelling preliminary data that suggest the practice may be associated with improving mood and energy,” Bower said. “Yoga also has been found to be helpful in easing symptoms related to multiple sclerosis and other disorders.”

Bower also is examining the impact of positive outcomes of stressful experiences such as cancer. “Many cancer patients report positive changes in self-concept and shifts in priorities, goals and relationships,” she said.

“We are hoping to identify physiological factors that contribute to this experience and the possible implications on physical health.” •



Chronic stress leads to increases in the formation of blood vessels around tumors (as shown by the red staining), which increases tumor growth and risk of metastases.

Thakker, P.H. et al. Chronic stress promotes tumor growth and angiogenesis in a mouse model of ovarian carcinoma. *Nat Med* 12, 939-944, 2006.

First Bhaumik prize awarded

The UCLA Cousins Center presented University of Wisconsin's Richard Davidson with its first Mani Bhaumik Award at a Nov. 16 ceremony.

The award was established in 2006 to support scientists in the international community who advance the understanding of the brain and the conscious mind in healing through visionary research, books and education. Bhaumik, co-inventor of the laser technology that made LASIK surgery possible, is funding the annual \$10,000 award.



Bhaumik

Davidson, Ph.D., the William James and Vilas Professor of Psychology and Psychiatry at the University of Wisconsin, is perhaps best-known for his research on neuroplasticity, the capacity of the brain to change throughout life. His pioneering research using brain scans of Tibetan monks provides tantalizing evidence that emotions like love and compassion are in fact skills that can be learned.



Davidson

Photo: Jeff Miller/University of Wisconsin-Madison

Bhaumik earned a Ph.D. in physics from the India Institute of Technology and a Sloan Foundation Fellowship for postdoctoral work at UCLA. ●

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infection-fighting white blood cells that promote healing. However, a variety of immune system disorders can cause the body to turn on itself, sometimes causing inflammation that can damage healthy organs and tissues.

The UCLA research team conducted blood and DNA analyses of 30 healthy adults drawn during the day across three set time frames and after a night of partial sleep deprivation.

The results show that white blood cells called monocytes produce significantly greater amounts of two

disease-fighting proteins that promote inflammation after a poor night's sleep compared with amounts found after a night of uninterrupted sleep.

This research was supported by the National Institutes of Health and the NIH General Clinical Research Centers Program. ●

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MINDBODYConnections

Winter 2007 Vol. 1 No. 1

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