



HEALTHWISE

UNIVERSITY of CALIFORNIA, SAN DIEGO SAM and ROSE STEIN INSTITUTE for RESEARCH ON AGING

JUNE/JULY 2007 • VOL. 26, NO. 4 • ONLINE AT SIRA.UCSD.EDU

SIRA'S PUBLIC LECTURES

JULY

Obesity and Aging

Elizabeth Barrett-Connor, M.D.
Division of Epidemiology
Department of Family & Preventive Medicine
Wednesday
July 18, 2007, 6:30 p.m.
Garren Auditorium
UCSD Basic Science Building,
University of California, San Diego
A description of this lecture topic appears on page 8 of this issue.

AUGUST

Sex, Aging, and Dementia

Daniel Sewell, M.D.
Division of Geriatric Psychiatry
Department of Psychiatry
Wednesday
August 15, 2007, 6:30 p.m.
Garren Auditorium
UCSD Basic Science Building,
University of California, San Diego
No reservations required.

Free parking is available.
Please call (858) 534-1226 AT LEAST THREE WORKING DAYS IN ADVANCE to receive your free parking permit. Attendees may also purchase permits at the parking kiosk on Gilman Drive or park at the metered sites.

Directions:
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• Left into Parking Lot 602 (first stop sign)
• From parking lot, walk towards Medical Teaching Facility (MTF)
• Right through MTF and enter Basic Science Building through glass doors
• Left down first hallway

Successful Cognitive Aging

Dr. Seuss
(from *Oh, the places you'll go!*, 1990)
You have brains in your head.
You have feet in your shoes.
You can steer yourself
any direction you choose.

When the topic of aging comes up on the news or in discussion, most often we hear about how the population is growing older by the minute. We also see examples of people living longer and healthier lives, redefining aging-related stereotypes, and changing our basic concepts about older people. Biomedical research in aging has made incredible strides over the past decades in understanding why we age. However, it is a relatively recent phenomenon that significant research has been directed at healthy aging, instead of focusing on the diseases and disabilities that older people experience.

At SIRA, our mission over the past two years has been to establish and encourage research on healthy or successful

aging. Understanding what defines and predicts the "healthspan" is a complex undertaking, necessitating contributions from basic sciences like neurobiology and genetics in tandem with clinical and social scientists like physicians and medical anthropologists. What we have found is that it is not hard to generate interest in this topic, but it is often difficult to know where to start. Based on a considerable amount of preliminary research, consultation with world-renowned aging researchers and community members, and just plain old time in the library, we have chosen to focus on successful cognitive aging. Cognition broadly refers to the ability to process information, apply it, and develop preferences or mental "maps" based on our experiences. This definition encompasses what we commonly think of in terms of cognitive abilities, such as memory and learning, but also our self-concept, the way we respond to positive or negative emotions, and our ability to manage our day-to-day affairs. We chose to focus

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The Prostate: Everything You Ever Wanted to Know, But Were Afraid to Ask

Dr. J. Kellogg Parsons

6/28 9:00 p.m.

6/29 11:00 p.m.

7/1 5:00 p.m.

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For clinical trials at UCSD: <http://health.ucsd.edu/ntrials/>

Successful Cognitive Aging

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SIRA's research on successful cognitive aging for three main reasons:

1) The future of aging will increasingly depend on brain health. At the turn of the twentieth century, the life expectancy of the average human in the industrialized world was about forty years, and infectious diseases were the primary cause of death. Once sanitary conditions were improved, chronic physical illnesses such as heart disease and cancer became the leading causes of our demise. Biomedical sciences have emerged to lengthen the survival of individuals with chronic physical illnesses or invent ways of preventing them. Remember that less than thirty years ago, cancer was not even considered a chronic disease! If these trends continue, a possible scenario is that neurodegenerative diseases and other brain-related illnesses, such as Alzheimer's disease, may become the prominent causes of disability in

aging. Scientists are just beginning to develop new treatments to prevent or delay these brain-related illnesses—this means that we need to act now to figure out ways to keep our brains healthy.

2) Much of what we know about successful aging depends on the brain. Aging science's current "best bets" in terms of increasing the healthspan involve lifestyle behaviors (physical and mental activities and diet), limiting stress and depression, and positive attitudes and beliefs. In order to change any of these factors, we need to start with the brain. For instance, research has shown that starting a moderate physical exercise program may increase brain volume in older people; discovering what motivates people to start an exercise routine, and stay with it, will necessarily involve understanding the cognitive processes involved.

3) UCSD is a worldwide hub for cognitive neuroscience. An incredible number of the scientists in UCSD's neuroscientific community are foremost in their respective fields, and they represent SIRA's most unique resource. Bringing these minds together with a communal focus on successful cognitive aging can allow for the kind of interdisciplinary and innovative research that is needed, and SIRA and UCSD are well positioned to do just that.

There is clearly much to learn about successful cognitive aging, and much that can be done to encourage it. We hope that SIRA will evolve into an international hub for research on successful cognitive aging.

—Colin Depp, Ph.D.
Department of Psychiatry

Neural Changes Underlying Decline in Working Memory Ability in Healthy Aging

As we age, we become a little worse at keeping and juggling information in mind. Scientists refer to this ability as working memory – the ability to maintain and manipulate information in mind for a few seconds in the service of a cognitive task. Remembering a new phone number long enough to dial it, or performing a mental arithmetic problem are examples of activities that require working memory. The reason for the decrease in working memory ability with age is not fully understood, although it is known that decreases in working memory ability can contribute to impairments in other cognitive functions.

To gain a better understanding of why working memory ability decreases with age, I am using advanced, noninvasive neuroimaging methods to examine the structural and functional changes in the brain that accompany the change in working memory ability with age

in healthy adults. I am investigating the hypothesis that decreased working memory ability arises from a disruption of synchronized neural activity between different brain regions caused by deterioration of the brain's white matter fiber tracts. Working memory requires the interaction of neural activity across a number of different brain areas, including areas in the frontal and parietal lobes. Deterioration of the fiber tracts that connect these areas may disrupt the ability of these brain areas to communicate effectively with each other, degrading the neural representation of information being kept in an active, available state.

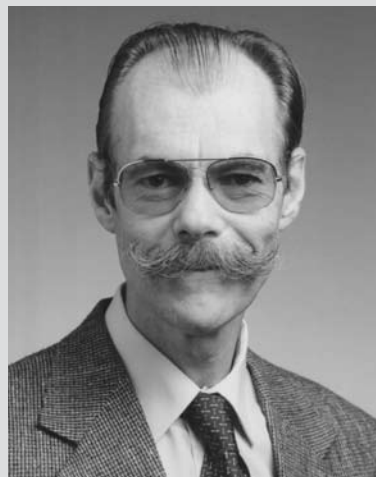
In this study, young and older participants undergo a form of magnetic resonance imaging, called diffusion tensor imaging, that allows quantification of the brain's white matter tracts. Participants also have their brainwaves recorded while they perform working

memory tasks, using a method called magnetoencephalography (MEG). MEG is a measurement of the small magnetic fields produced by neural activity. These fields can be measured by having participants sit under a device that contains sensors that are highly sensitive to magnetic fields.

I will investigate whether age-related decreases in the integrity of the white matter tracts that connect the frontal and parietal areas is associated with a decrease in the synchrony of neural activity between these regions that occurs while participants hold information in memory. Understanding the changes in the brain that underlie the reduction in working memory ability with age is a necessary first step to developing methods to prevent or minimize these changes.

—Linda McEnvoy, Ph.D.
Department of Radiology

In Memory of Leon J. Thal, M.D., 1944–2007



Distinguished professor and chair of neurosciences at UCSD School of Medicine, and one of the world's leaders in the development and study of new therapies for Alzheimer's disease, Leon J. Thal, M.D., was killed in a plane crash February 3, 2007. Dr. Thal, sixty-two, was piloting a plane between San Diego and Borrego Springs, California.

An expert on memory loss, cognitive defects and gene therapy, Dr. Thal directed the Alzheimer's Clinical Trials group, an NIH-funded nationwide consortium of more than seventy centers that test experimental therapies for Alzheimer's disease. He also served on the National Institute of Aging Advisory Council (2002–2006) and as a permanent advisor

on the FDA anti-dementia assessment team. In addition, he managed UCSD's Shiley-Marcos Alzheimer's Disease Research Center. Dr. Thal oversaw more than \$100 million in federal research grants and was a collaborator on many others. He and his department had received millions of dollars in research funds over the past thirty years.

Dr. Thal was born in New York City in 1944. He earned a medical degree from the State University of New York's Downstate Medical Center in Brooklyn and received his neurology training at the Albert Einstein College of Medicine in the Bronx. He took a job at UCSD in 1985 as an associate professor of neurosciences. In 1993, he was named department chairman. In December 2004, Governor Arnold Schwarzenegger appointed Dr. Thal to serve on the Independent Citizens Oversight Committee of the California Institute for Regenerative Medicine, which was created when voters approved Proposition 71, the California stem cell initiative. Schwarzenegger said in a statement issued upon hearing of Dr. Thal's accident, "Today, Maria and I were saddened to hear the news of Dr. Leon Thal's death." His many other hon-

ors include receiving the Arthur Cherkin Memorial Award in 2003, and the Potamkin Prize for Research in Pick's, Alzheimer's, and Related Diseases in 2004. The Potamkin Prize, one of the nation's highest honors in neurosciences was given to Dr. Thal for his work showing that inhibiting an enzyme called cholinesterase could stall progression of Alzheimer's in patients with the earliest symptoms and for bringing collaborators together to work on the disease. Recently, prior to his death, Dr. Thal was named to the board of the National Alzheimer's Association, which routinely gives grants to promising areas of dementia research. He also was involved with several U.S. Food and Drug Administration panels charged with evaluating grant applications.

Dr. Leon Thal's colleagues described him as affable and disarming, a skilled diplomat who could steer headstrong researchers toward a common goal. "Dr. Thal wore a signature, handlebar-style moustache and stood well above six feet tall," Dilip Jeste, M.D., a longtime colleague and personal friend of Dr. Thal's and director of SIRA, said in an interview; "He was a towering personality. If you saw him once, you'd

never forget him." That would certainly be the case among dozens of students and junior faculty members who worked with him, Dr. Jeste said. "When you talked to him, you never felt you were talking to some big shot. He would talk to a student the same way he'd talk to the chancellor."

Dr. Thal was remembered by his friends and colleagues at a standing-room-only memorial at UCSD on March 5, 2007. In honor of Dr. Thal's commitment to the training of promising neuroscientists, the "Leon J. Thal Educational Fund in Neurosciences" has been established. Donations to this fund can be made online at <http://neurosciences.ucsd.edu/neuro-central/memorial.htm>, or checks may be made payable to UC San Diego Foundation, referencing Fund #4467, Thal Educational Scholarship (on memo line of check) and sent to:

UCSD Department of Neurosciences
c/o Leon J. Thal Educational Scholarship Fund
9500 Gilman Drive, # 0853
La Jolla, CA 92093-0853

Looking Back and Looking Ahead: A View from a Departing Member of the Community Board of Advisors



Gregory Stein, M.D.

It seems odd, in a sense, that I would be sitting here excitedly writing about an organization that I am about to leave, but the perspective of eight years of service on the Community Board of Advisors (CBOA) to the Sam and Rose Stein Institute for Research on Aging puts me at a vantage point where I can marvel at what has evolved and confidently speak of what is planned for the months and years ahead. My departure from the board is in no way a reflection on the organization, but rather it is the result of increasing demands from new business ventures and, after eight years on the board, it is time to make way for some new faces who will

hopefully add to the wonderful group of community volunteers with whom I have had the pleasure to work.

My tenure on the CBOA began when I returned to San Diego in 1999 to pursue a new career opportunity. As the grandson of the major benefactors of the institute and a physician with eleven years of experience practicing medicine, I felt that joining the board made sense for a variety of reasons. First, it offered me an opportunity to continue to support an organization about which I know my grandparents felt passionately. Their philanthropic investment philosophy was to support causes focused on either end of life's journey, namely, children and the elderly. SIRA, with its mission to support cutting-edge research in areas related to aging, fit in well with that philosophy. Second, it was, in a way, a chance to help steward the investment that they made in this organized research unit within the School of Medicine. My participation on the board would allow me to take part in guiding the organization and ensuring that my grandparents' vision continued to be realized. Finally, given my medical background, I would be in a unique position to help facilitate a dialogue among the clinical and research faculty, the CBOA and the community.

Over the past eight years, both the CBOA and the institute have evolved significantly. The board has come to take on a much more active role in fund-raising as well as communicating the story of SIRA to the community. The advisory role still exists to some degree, but the board has made it its mission to expand the donor base supporting the organization, increase charitable giving amongst both the board and the community at large, and expand awareness of the work that SIRA is doing through a variety of activities. These have included helping to fund a major marketing study that helped to clarify how best to communicate the SIRA story to a number of different groups with a stake in SIRA-sponsored research, hosting events for friends and associates to learn about some of the cutting-edge research being done by SIRA-affiliated faculty members, and organizing a community outreach program called "Lunch-and-Learn," which brings relevant and exciting information to many local community groups. The board now comprises a capable and committed group of community volunteers who have consistently demonstrated their support for SIRA.

SIRA has always had strong leadership. Jay Seegmiller, M.D., was the first. His vision led to the creation of SIRA and his commitment and devotion to the organization continued unabated for many years, even after he had officially left his academic post within the medical school. Jay was a kind, thoughtful, and passionate scientist and it is a pleasure to say that I had a chance to know and work with him before he died. Dr. Dennis Carson, who directed SIRA for thirteen years, succeeded Dr. Seegmiller. Under Dr. Carson's direction, countless grants were awarded to medical students and junior faculty looking for an opportunity to test their ideas in areas related to aging.

Oftentimes the research done with a SIRA grant would lead to much larger grants from the NIH and other major sponsors of academic research. Without the pilot grant money from SIRA, many of these larger grants would not have been possible. Most recently, SIRA has been fortunate to have Dr. Dilip Jeste as its director. Within the short span of three years, Dr. Jeste has significantly expanded the staff and added a Scientific Advisory Board as well as an External Advisory Board of top scientists from around the country. New programs include the Medical Student Training in Aging Research (MSTAR), the High School Student Training in Aging Research (HS STAR), monthly grand rounds, and a journal club for the medical school faculty and students, multiple SIRA-run research studies and publications in the area of successful aging, and the addition of important clinical and research fellowships in geriatric medicine. If SIRA continues at its current pace on the course that Dr. Jeste and his team have mapped out, I have little doubt that SIRA will soon achieve its vision of becoming a nationally recognized leader in the area of successful aging research.

So, it is with mixed emotions that I step down from my position as a member of the CBOA. My tenure on the board has been tremendously rewarding as well as a wonderful learning experience. Everyone affiliated with the organization has, in his or her own way, played an integral part in bringing SIRA to the place in which it now finds itself, which is truly a major inflection point in the organization's evolution. I am proud to have played my small part in reaching this point, and I look forward to seeing the dedicated staff and volunteers drive SIRA to new heights. I want to thank everyone for allowing me to be a part of this journey and wish you all nothing but the best in achieving your goals in the years ahead.

—Gregory Stein, M.D.

SIRA Junior Faculty Pilot Grants: the Next Generation of Discovery

Elias A. Zerhouni, M.D., the director of the National Institutes of Health (NIH), has articulated a new vision for medicine: an approach that is predictive, personalized, preemptive, and participatory (*NIH Medline Plus*, Winter 2007, pp. 2–3). This individualized approach contrasts with what Dr. Zerhouni calls the one-size-fits-all approach to medicine that is available today. This revolutionary approach builds upon new understanding of mechanisms of health and disease that we have from the Human Genome Project, innovations in imaging technologies, and new findings in the social and behavioral sciences.

SIRA's research program, with its focus on successful cognitive aging, is a realization of Dr. Zerhouni's vision. Nowhere is this more apparent than in SIRA's Junior Faculty Pilot Grant program, now in its second year. Pilot studies are the "proof of principle" investigations that demonstrate scientific feasibility. These small, highly innovative experiments are the building blocks for research programs. The goal of SIRA's program is to support new scientists in the preliminary studies they need in order to justify larger scale support of research from an external funding agency such as the NIH

or a private foundation. We solicited innovative research project grant applications from junior faculty members at UCSD and associated institutions. First priority was given to applicants with projects focused on successful cognitive aging in humans or animals. We established formal evaluation criteria similar to those used in national research programs and limited the proposals to one year in duration and \$10,000 in support. SIRA's Scientific Advisory Board reviewed the applications and we were able to support the work of seven young investigators. This year's recipients included: Liat Ayalon, Ph.D., Jacqueline Kerr, Ph.D., Julie Wetherell, Ph.D., Linda McEvoy, Ph.D., Alan Nagahara, Ph.D., Victoria Risbrough, Ph.D., Chih-Min Tang, Ph.D., and Dianne Langford, Ph.D. We are highlighting two of them in this issue, and will feature others in future issues. As would be expected from a scientific environment as rich as UCSD's, the projects have an amazing diversity of approaches and scientific disciplines. Some of the studies begin at the most fundamental level of molecular medicine and genetics while others move to the development of biomarkers by using the technologies of brain imaging and pharmacology, and

others investigate behavioral and physiological aspects of aging. These new investigators use animal models, tissue samples, and human participants in their research. The highest ethical principles for protection of human and animal research participants are followed in these studies.

We are proud of the contribution SIRA is making to career development of scientists whose work will lead to greater understanding of successful aging, health, and disease. Support for the Junior Faculty Pilot Grant program, and other research and training programs of SIRA is made possible by the annual financial contributions of over 600 San Diegans. All of us at SIRA are grateful for their support and for the vote of confidence they have made in our programs. In reading about the research of these new investigators, and the promise that it contains for the development of a new, individualized approach to medicine and successful aging, we hope that others will join their neighbors as active contributors to SIRA. Information about contributions is included in this issue.

—Barry D. Lebowitz, Ph.D.

The Genetics of Age-Associated Neurocognitive Decline Using Inbred Mouse Strains: Development of an aging-sensitive behavioral test battery

Rodent models have helped us understand the functional consequences of many genetic mutations, including learning and memory. Animal research has focused on developing models of many diseases' states and dysfunctions that can occur as we age, particularly declines in learning and memory abilities. Few studies have focused, however, on modeling some people's resistance to aging effects. Why do some people have relatively intact activity and mental abilities while others experience the more common gradual decline in certain mental processes? Interestingly,

rodents appear to have the same varied response to aging as humans. Recent research has shown that in laboratory rats, some show normal decline in memory abilities; however, some are resistant to aging effects, and look similar to young rats in their memory performance. In humans, many complex interacting factors are likely to be involved in resistance to the damaging effects of age on cognitive processes, including social network, level of life stress, nutrition, and genes. Many of these factors are difficult to model in animals. Nonetheless, rodents can be useful in understanding how

certain genes may affect aging, and may help us discover genes that are important for resistance to age effects on brain functions.

My research uses behavioral mouse models to identify potential genes involved in resistance to cognitive decline. Small differences in gene sequences can cause a number of different possible effects, two of which are changes in how much the gene is "expressed," resulting in changes to how much peptide is produced by that gene. Gene mutations can also cause changes in the peptide

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New Faces at SIRA

We are pleased to announce that our SIRA staff is expanding. Three new staff members have joined our team in the last several months. Jody DeLaPena Murphy has joined the staff as the director of Community Relations. In this newly appointed position, Jody's primary responsibility is to plan and direct the SIRA grand rounds and public lecture series, oversee the *Healthwise* newsletter and SIRA Web site, and work with the Community Board of Advisors to enhance the information exchange between SIRA and the community.



Jody will graduate in the fall of 2007, with a master's degree in business administration with an emphasis in organizational leadership. She has been working in the UCSD Department of Psychiatry for over fifteen years. Jody began in 1992, coordinating memory studies for the late Nelson Butters, Ph.D., who was the Veterans Administrative Medical Center's Chief of Psychology at that time. In 1998, she took a position with

Dr. Dilip Jeste as the recruitment coordinator at the Research Center in Geriatric Psychiatry. She served as a community health program manager for the center for several years prior to her departure, and worked extensively on establishing and enhancing the community partnerships that were so important to the work of the Advanced Center for Innovative Services and Interventions Research.

Jody's extensive research experience combined with her interest in community relations make her an excellent candidate for the SIRA's director of community relations, and we are pleased to have such a well-qualified and enthusiastic person for this new position. If you have any questions for Jody, please do not hesitate to contact her via email at jodelapena@ucsd.edu or at (858) 822-1132.



Troy Shivers began his career in Web designing at the University of San Diego in 1991, in what was then known as Information Management, integrated with USD Development fundraising. His work was partitioned into three main areas, all supporting faculty, staff, and students at varying levels. He was specifically involved in the areas of training and Web support and design.

With his ten plus years' experience in Web designing, he was given the opportunity to become involved in creating Web sites for the Donald P. Shiley Science and Technology Building and the Degheri Alumni Building. He also played an integral role in "History in the Making," the 1993 Presidential Debate in San Diego between Bill Clinton and Bob Dole where Internet Web video streaming was used for the first time to encourage young generations to vote. To this day, the Web is a critical tool in reaching out to young voters in the political world. Now, working for SIRA as our Webmaster, Troy hopes to push the envelope in technology by bringing medical research, video streaming, and other online information to UCSD faculty members and the community.

"I'm thrilled to say that I really enjoy what I do," expressed Troy in an interview. "I'd like to think that I make people's lives easier by supporting their technological needs. I feel very much appreciated and am ever so grateful to work with amazing people who also enjoy their work. After working briefly in the corporate world, I learned that my niche is most definitely in academia, where it's easy to find people with a willingness to learn."

Steve Jobs once said to the graduates of Stanford, "You can't connect the dots looking forward; you can only connect them looking backwards. So you have to trust that the dots will somehow connect in your future. You have to trust in something—your gut, destiny, life, karma, whatever. This approach has never let me down, and it has made all the difference in my life. Stay Hungry. Stay Foolish." From his past experience with technology, interactive media and traditional graphic design, Troy hopes to continue to do what he enjoys and bring the innovation and expertise that is needed for a successful visual site to SIRA.



Tabitha Kirkland first became involved with SIRA nearly two years ago as a part-time data entry assistant while she was a student at UCSD. After the position ended, she continued her studies and worked as a research assistant to Lori Montross, Ph.D., in the Geriatric Psychiatry Department. She graduated in June of this year with a B.A. in psychology with honors. We are fortunate to have her back at SIRA as a full-time research coordinator. Tabitha's long-term goal is to earn her doctoral degree in social psychology and hold a faculty position at a college or university. In her free time she enjoys yoga, reading, cooking, and planning European adventures.

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We would like to express our deep appreciation for all those listed, as well as the anonymous donors, who chose to provide support to the Sam and Rose Stein Institute for Research on Aging during December of 2006 and the first half of 2007.

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The Genetics of Age-Associated Neurocognitive Decline Using Inbred Mouse Strains continued from page 5

sequence itself, which may change the peptide's ability to function. Thus differences in behavior or disease resistance may be due to changes in peptide function, or possibly in the amount of peptide that is available to the cell, decreasing or increasing its functional output. There are currently forty-eight common laboratory inbred mouse populations, where each population can be considered a population of identical twins. Thus each strain can be studied in perpetuity while having a relative fixed genetic background. Many databases exist or are being rapidly compiled of how these inbred strains differ in the amount of gene expression in certain tissues (including the brain), likely due to differential mutations in small portions of the genome across these strains. In addition, numerous studies examining the differences in behavior and physiology across these strains have been conducted. Thus there is now a large amount of information on how these strains differ

genetically and behaviorally. Yet the vast majority of these studies have focused on young adult mice and most studies have not studied age-related changes in these behavioral and physiological measures. I am developing a behavioral test battery to screen inbred mouse strains for aging effects on cognition. The battery will include tests of many different types of learning and memory that may be affected by age. By using such a screen I hope to identify inbred mouse populations that show resistance to cognitive decline associated with age. Once strains that have differing age-dependent cognitive decline are identified, studies of which genes may cause these differences will be conducted, including examining differences in gene expression levels in the brain that correlate with changes in memory ability with age.

—Victoria B. Risbrough, Ph.D.
Department of Psychiatry

Jump-Start Your Legacy With a New Tax-Saving Opportunity for IRA Owners...

You may be interested in the recent changes made through the Pension Protection Act of 2006. Of special interest is the provision that allows tax-free distribution of up to \$100,000 per year from Individual Retirement Accounts directly to qualified nonprofit organizations, including the UC San Diego Foundation. While no charitable income deduction accompanies the transfer, the distribution directly to the charity is not included in taxable income. Gifts must be completed by December 31, 2007, and the owner of the IRA account must be age seventy and one-half or older by the date of the contribution.

This is an excellent opportunity to give to The Sam and Rose Stein Institute for Research on Aging (SIRA) at UCSD! If you have any questions or would like a free copy of our brochure, *How To Make Charitable Gifts From Your IRA*, please contact Geoff Graham, at (858) 534-2249, or visit our Web site at www.planned-giving.ucsd.edu.

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* *in memoriam*

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Obesity and Aging

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Dr. Barrett-Connor will be speaking on this topic at the SIRA Public Lecture on July 18. Please refer to page 1 of this issue for more information.

Abstract: A review of the prevalence and demographics of obesity and metabolic syndrome in the US will be presented, as well as current knowledge about the physiology of these conditions and findings pointing to a mechanistic link between obesity and inflammation.

Discussion points on obesity, the metabolic syndrome, and dementia illustrating one or more methodological problems are listed below:

- Selection of the original cohort—criteria and representativeness
- Loss to follow-up
 - Selective attrition by death or cardiovascular disease often due to obesity-related conditions
 - Selective loss of demented participants
- Diagnosis of dementia or memory loss
 - Type of dementia: primary or secondary; senile dementia of the Alzheimer's Type or vascular
 - Too many cognitive function tests of low sensitivity
- Diagnosis of obesity by BMI—would waist girth, sagittal diameter, or visceral adipose tissue be better?
- Diagnosis of the metabolic syndrome is a moving target
 - Present in > 90% of overweight diabetics
 - Loss of information with categorical variables
- Should we adjust for diabetes and metabolic syndrome?
 - Most obesity studies in the elderly have no oral glucose tolerance test, can't rule out diabetes, the myth of the independent association
 - Is metabolic syndrome w/o diabetes in the causal pathway?
- Inflammatory markers are increased in obese
 - An independent association?
 - In the causal pathway?
- Unknown time of dementia onset, which limits time-to-event analyses
- The effect of interim treatment for blood pressure, lipids, etc.
- Can we use existing cohort data to do better?
- Can weight loss trials address these questions (e.g., Women's Health Initiative, Diabetes Prevention Program—well-known study/program—much in the med. literature/news . . .)?

For clinical trials at UCSD: <http://health.ucsd.edu/ntrials/>

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