

CONTENTS

Research News **Healthy Aging**

Estrogen & Exercise

Successful 2-3 Aging

Clinical Trials 6

Donor Spotlight 7

Memory Walk Highlights 9

Family Education Series 10

Calendar 12

Brain Aging is the newsletter of the Institute for Brain Aging & Dementia, a nonprofit Institute dedicated to improving the lives of those afflicted with Alzheimer's disease through research and education.

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DIAIN A Bulletin University of California, Irvine

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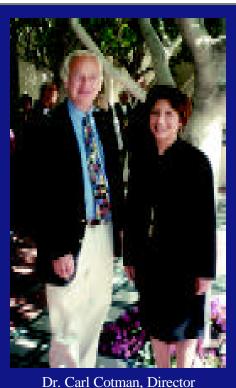
Institute Welcomes Claudia Kawas, M.D.

Dr. Claudia Kawas is an internationally distinguished Neurologist known for her clinical expertise and her research on the causes and treatments for Alzheimer's Disease. Dr Kawas accepted a position at the Institute for Brain Aging in October after completing a 9 month sabbatical at UCI in early of 2000.

"We are indeed honored and excited about Claudia joining the research program on brain aging and Alzheimer's disease. It is a great tribute to the program, the community, and the University to have her here. She had many other offers and we are thrilled about her decision to join UCI. I am confident her efforts will greatly enhance our program." says Dr. Cotman, Director of the UCI Institute for Brain Aging & Demen-

With a longstanding interest in research on aging and dementia Dr. Kawas came to UCI from Johns Hopkins School of Medicine, Baltimore, Maryland where she was Director of Geriatric Neurology for 15 years and conducted longitudinal studies of normal aging and clinical trials.

Dr. Kawas has been appointed the Director of the Alzheimer's Disease Clinical Research Program here at UCI. "I look forward to developing research in the determinants of successful aging, the cognitive and functional abilities of the oldest old, over 90 years of age, and the prevention of Alzheimer's disease.", Dr. Kawas commented.



and Dr. Claudia Kawas. Clinical Research Director

"She is extremely versatile. Her work includes diagnostic clinical work, research on the risk factors for AD, treatment of Alzheimer's disease and relationships between clinical and the neuropathological basis of brain aging and Alzheimer's disease.", says Dr. Cotman.

She has shown, for example, that the use of non-steroidal anti-inflammatory drugs reduces the risk for Alzheimer's disease.

Kawas Continued on Page 2



Successful Aging Program:

A Partnership for Discoveries on Healthy Aging

Julene Johnson, Ph.D.

Once upon a time, most people believed that getting older was associated with a gradual "downward slide" of both physical and cognitive abilities. Then one by one, individuals who were aging gracefully appeared on the doorsteps of scientists and finally convinced them to study how and why some people function extremely well into advanced age. We listened to these folks, and in 1994, the Institute for Brain Aging and Dementia at UC Irvine founded the Successful Aging Program. The purpose of the program is to study the cognitive and brain characteristics that are associated with healthy aging. The Successful Aging Program is supported by an Alzheimer's Disease Research Center grant from the National Institutes on Aging.

There are currently 225 healthy seniors who are enrolled in the Successful Aging Program.

Many of the participants live in Laguna Woods and Regent's Point or participate in Oasis (Newport Beach) and range in age from 48 to 96 years. Each successful ager participates in an annual battery of tests that evaluates learning and memory, language, and visual-spatial skills. The results from these tests help us to understand what happens to language and memory skills throughout the lifespan. The successful agers also agree to donate their brains after passing so that researchers can also study the cellular changes that occur with healthy aging. Being able to study brains of individuals who have been studied for many years provides invaluable clues and hints about aging successfully.

With the recent recruitment of Dr. Claudia Kawas, an internationally known researcher on healthy aging, we plan to ex-

pand the research on healthy aging. Specifically, we will focus on folks who are over 85 years of age because we have the least amount of information about what happens in the 8th and 9th decade and beyond. We are very excited to

learn more from these "super successful agers". It is only through partnerships like this that we are able to make important future discoveries about the mysterious phenomenon that we are all doing: AGING.

A Great Ager

Mrs. Mary Betsey Gamer (93 years young), has been a participant in the Successful Aging Program since 1995. She credits her successful aging to 30 years of transcendental meditation. After taking a course on the topic, she began meditating twice a day and has not stopped since then. She also gives a lot of credit to her cat Muffin who is her "joy". After the death of her husband, she adopted Muffin who was an abused cat. Once Muffin left enough clues that he was a true "outdoor cat" (i.e., eating phone cords and screens), they got along fabulously. "I had to be 87 before I got a pet.", she says with a twist of wit. Mrs. Gamer also enjoys an active concert schedule and attends 3 concert series including the LA Philharmonic. She also participates in several clubs in Laguna Woods such as the Cat

Mary Gamer, Successful Aging Participant -photo by Ed Gray

.

Club and Garden Club.

Mrs. Gamer has never enjoyed exercise. In fact, she says that she is a "born couch potato". In her younger years, she stayed at home and knitted for exercise. But after an angioplasty, she began following a Dean Ornish's exercise and diet recommendations. She went to the gym 3 times a week and maintained a good diet.

Another striking characteristic about Mrs. Gamer is her witty sense of humor and positive attitude. She says, "I have never gotten arrested. I'm not mad at anybody. I'm not prejudiced."

Mrs. Gamer was born in St. Louis, Missouri in 1907 and graduated from Washington University in 1929. She was an elementary school teacher. She was also married for 63 years and has 2 children.



Outstanding Community Friend Joyce Tucker is Recognized

Successful Aging volunteer staff member Joyce Tucker has been chosen to receive the Lauds and Laurels Award for Outstanding Community Friend by the UCI Alumni Association for the year 2000. Joyce has been volunteering with the Successful Aging Program at the Institute since 1994 when there were as few as 20 healthy control subjects who needed annual assessment. Joyce conducted assessments, scored results and recruited participants. Due to her diligence, the program has grown

to a control population of 300.

When Carl Cotman first met with Joyce to see if he might have a volunteer opportunity that would interest her, she stressed that she wanted to do



something significant. "We provided that opportunity and she in turn has performed a job far more comprehensive than we ever imagined possible. She is creative, dedicated and energetic. More than that she is incredibly generous with her time and resources. She gives from her heart and puts everything behind her conviction in order to make a difference. I challenge you to show me any volunteer more deserving of this award.", says Cotman, Director of the Institute for Brain Aging & Dementia.

Joyce was nominated for the Lauds and Laurels award by Dr. Cotman and the Dean of the UCI College of Medicine, Thomas Cessario, who commented, "The Health Sciences area has been fortunate to have many tireless volunteers who are willing to work diligently and cheerfully over the years. However, few stand out as brilliantly as Joyce does,

with her enthusiastic 'can do' attitude and her unstoppable sense of initiative. Dr. Cotman and the staff of the Institue for Brain Aging speak frequently with gratitude and respect for Joyce's good work. We realize that there are many worthy causes to which Joyce might turn her attention. We are grateful that she has chosen to dedicate her time, her creativity and her heart to help advance our understanding of healthy aging."

Joyce's willingness to visit and test many "successful agers" in their homes has contributed to the success of this program, as many individuals would not participate if they had to drive to campus. Joyce spends a considerable amount of time with these individuals, getting to know them and learn about their lives. Her willingness to go the extra mile and her genuine concern for these people are invaluable to our program. Without Joyce's dedication during the past 7 years, the Successful Aging Program would never have succeeded. It is timely and suitable that Joyce be recognized for her efforts. Congratulations Joyce! From the entire staff at the UCI Institute for Brain Aging & Dementia.

Dr. Johnson Receives Award from the Alzheimer's Association of Orange County for her Contributions to Research on Frontal Temporal Dementia and Development of Support Group for Caregivers



Dr. Johnson, Kim Bailey, Linda Scheck & Dr. Cotman



A Special "Goodbye" to all of my F riends!

Over the past 7 years with the UCI Alzheimer's Disease Research Center and Institute for Brain Aging I have been fortunate to establish many wonderful relationships with an amazing group of researchers, clinicians, staff and families. My experiences at UCI as a whole have shaped my life in many ways and the memories of patients and their families will be unforgettable to me. It is, however, with both happiness and sadness that I must say "farewell" to my friends and family at UCI. I am very excited to say that my new home will not be far away at the Alzheimer's Association of Orange County. My new role as Director of Communications will afford me the opportunity to continue to promote the state-of-theart research and clinical programs conducted at the Institute for Brain Aging and Dementia. I am looking forward to working with my UCI collegues and the many families I served during my tenure in a slightly different capacity. Since many folks have already inquired, I do plan to co-captain the UCI Team at the annual Memory Walk in 2001. I hope to see you there!

-Elizabeth Eastin

Clinical Trials Update

Currently Enrolling Trials

For Men Only: Testosterone Trial

A new preparation of **Testosterone** gel, available in a patch form, will be tested for its ability to improve cognition (mental processing) in male patients with Alzheimer's disease. Simultaneously, we will be testing the ability of the compound to improve memory and cognition in normal male control subjects who do not have Alzheimer's disease.

For Women Only: Estrogen Prevention Study

We are fortunate to be opening a prevention study that is part of a federally funded study from Columbia University, in which women with a family history of dementia are randomly assigned to estrogen replacement therapy versus no therapy for a period of three years. This study builds upon our previous research (that was published in February 2000 in JAMA) that clearly showed the lack of effectiveness that estrogen therapy had for women with a mild to moderate stage of Alzheimer's disease. The question that remains to be answered by this new study is whether estrogen can prevent the onset of Alzheimer's disease in women who are susceptible to the disease by family history. For this study we are looking for women at least 65 years of age who are not taking estrogen replacement therapy, and who have a family history of dementia in a first degree relative. Once enrolled in the study, women will visit our clinical site every 6 months for the three-year treatment period for follow-up. Clinical evaluations with memory testing at one-year intervals will allow us to monitor the benefit that estrogen therapy may

For more information on clinical trials at our center, please contact Catherine McAdams-Ortiz, RN, MSN, GNP (949)824-8726 or Hyunmie Kim, RN, MSN,

GNP at (949) 824-8136.

have for these women. If interested, please

contact our Clinical Trials Coordinator.

Ms. Ortiz at (949) 824-8726.



What is Normal Aging?

Article by Liz Head Institute for Brain Aging & Dementia

ne of the important questions being studied at the Institute is what constitutes normal brain aging and how normal aging is different from the development of Alzheimer's disease. We and others have looked at tissues from a number of healthy elderly control individuals, including several samples from people over the age of 100 years.

It is becoming increasingly clear that individuals with no pathology, including a lack of neurofibrillary tangle formation and senile plaque accumulation, is relatively rare. Indeed, most individuals over the age of 70 years have some mild pathology. What is interesting is that the extent of this pathology does not reach levels of that seen in Alzheimer's disease; healthy individuals appear to be able to slow the accumulation of pathology and neurons remain healthy despite existing mild pathology. This is striking because even the brains of individuals over the age of 100 years resemble those of individuals 30 years younger! Why is this the case? There may be a number of factors influencing successful brain aging. It is possible that the brains of normal individuals are able to absorb and implement countermeasures to deal with existing pathology. For example, individuals achieving higher education levels or who engage in intellectually challenging activities show a lower risk? Or lower age of onset.

Further, these findings suggest that factors such as exercise, estrogen replacement therapy, antioxidants and/or anti-inflammatories may not only serve as a potential treatment for AD but also may prevent the development of further pathology and promote successful brain aging. Additional epidemiological studies, clinical trials and interpretation with respect to existing brain pathology will provide us with a clearer understanding. The continued support of the community in our Successful Aging Program provides crucial information that helps our scientists identify important factors to promote healthy aging and to prevent Alzheimer's disease.

2001 Annual Alzheimer's Disease Research Conference

Alzheimer's Disease Research: Diagnostic Subtypes, New Treatments, and Hope for Prevention

May 11, 2001

Topics will include:

- Differences in Symptoms and Care of Alzheimer's Disease, Frontotemporal Dementia and Dementia with Lewy Bodies
- Amyloid vaccine: Possible New Therapeutic Intervention for Alzheimer's Disease
- Prevention Studies in Alzheimer's Disease
- •Case Presentations: Early changes, pathological changes

Speakers include:

Dale B. Schenk, Ph.D. •Claudia Kawas, M.D.•Cordula Dick-Muehlke, Ph.D.• Malcolm Dick, Ph.D.• Carl Cotman, Ph.D.• Arnold Starr, M.D.•Ron Kim, M.D.• Steven Potkin, M.D.•



Hosted by:



UCI Institute for Brain Aging and The Alzheimer's Association of Orange County

For more information or to register, please call 714-283-1111



Abstract Title: Estrogen and Exercise interact to regulate BDNF mRNA in the hippocampus.

N.C. Berchtold*; C.J. Pike; P. Kesslak; C.W. Cotman.

Both exercise and estrogen provide multiple health benefits, including protection against osteoporosis, improved cardio-vascular health, stabilized mood, and improvement in cognitive function. Because of the beneficial effects on cognitive function, we have investigated how estrogen and exercise can interact to regulate brain-derived neurotrophic factor (BDNF), a molecule that affects brain health and is important in learning and memory.

1) What are our findings?

Studying rats, we have found that estrogen and exercise both increase gene levels of BDNF in the hippocampus, a brain structure that is critical for learning and memory. In addition, we have found that estrogen itself stimulates physical activity.

In the absence of estrogen, such as occurs in menopause, BDNF levels decrease to about 60% of normal levels in the hippocampus. Previously we have found that several days

of exercise can increase BDNF levels in the hippocampus. Unexpectedly, this effect of exercise is lost when estrogen has been absent from the body for a long time. On the other hand, estrogen-replacement therapy for several weeks restores BDNF levels in the hippocampus. In addition, when animals are allowed to exercise while receiving estrogen-replacement therapy, BDNF levels increase further than with either treatment alone (exercise or estrogen-replacement), in some regions of the hippocampus.

An unexpected finding from this study was that the level of estrogen effects physical activity. Specifically, when estrogen levels are low or absent, animals exercise less than animals with normal levels of estrogen. However, when these estrogen-deprived animals received estrogen-replacement therapy, their activity levels increased back to normal levels within a few days. Thus, exercise and estrogen may be part of a positive feedback loop that provides combined benefits to ensure the maintained health and functioning of the brain, as shown in the diagram below.

2) Why are these results new and interesting?

These findings are exciting because BDNF improves the health and functioning of neurons, and is important in learning and memory. When BDNF levels decrease, neurons are more susceptible to injury, particularly neurons in the hippocampus, and learning and memory are impaired. In fact, BDNF levels are decreased in Alzheimer's disease, a disease where neurons in the hippocampus become impaired and die. Our study shows that levels of BDNF are increased by both exercise and estrogen, two factors that are important for maintaining good physical and mental health with aging.



New Support Group

for Caregivers of Patients with Lewy Body Dementia

An educational and support group for caregivers of patients with Lewy Body dementia began to meet in June of 2000 and will meet monthly on the first Wednesday of each month at 9am on

the UCI Campus. Co-facilitators are Kim Bailey of the Alzheimer's Association of Orange County and Elizabeth Eastin of the UCI Alzheimer's Disease Research & Treatment Center. For more information about the group, please contact Elizabeth Eastin at (949) 824-8135.



3) How are our findings important clinically?

Our finding that BDNF decreases in the absence of estrogen is important clinically, because in women, estrogen levels drop at menopause. Furthermore, our research shows that there is a "double-negative" effect of low estrogen, because in the absence of estrogen, exercise can no longer increase BDNF levels. Interestingly, our research suggests that part of the beneficial effects of estrogen on physical and mental health is indirect, via increasing physical activity and interaction with the environment. In fact, there is a large clinical and epidemiological literature that is consistent with this novel view on the mechanisms underlying beneficial effects of estrogen.

4) These findings confirm and expand upon previous work by ourselves and others:

These findings have been submitted in a manuscript, which is currently undergoing review for publication. Our observations that estrogen-deprivation decreases and estrogen replacement increases hippocampal BDNF gene expression levels confirm previous reports on the regulation of BDNF by estrogen. In addition, we have previously reported that exercise increases BDNF gene expression in the hippocampus in normal adult male rats.

There are several novel findings from this study: 1) exercise increases BDNF levels in female animals, similar to the effect of exercise that we have previously reported in male animals, 2) long-term estrogen deprivation disrupts BDNF gene regulation by exercise, such that the beneficial increase in BDNF with exercise is lost. Finally, 3) estrogen itself increases exercise levels, and the combined effects of exercise and estrogen-replacement therapy interact to modulate BDNF gene levels in the hippocampus.

5) Procedure:

For our study, we removed the ovaries from adult female rats in order to reduce estrogen levels and produce a condition similar to menopause. Control animals underwent the same surgery procedure but the ovaries were not removed. Three weeks after surgery, animals received continuous hormone replacement therapy with 17-beta estradiol or placebo for either 5 days or 4 weeks. Half of the animals were

assigned to a sedentary group, and half were assigned to an exercising group. Group sizes were 10 animals per condition, on average. For the last 5 days of hormone treatment, a running wheel was placed in the cage of each exercising animal, and the animals were free to use the exercise wheels at will. A computer monitored the distance that each animal ran per evening. Animals ran approximately 1-5 kilometers per evening. BDNF gene activity was analyzed using in situ hybridization.

6) The next steps in this research include the following directions of research:

A) How do longer periods of estrogen-deprivation affect BDNF gene regulation? Can estrogen replacement therapy restore BDNF gene levels after very long periods of estrogen deprivation? This is an important question, because many women wait several years after menopause before undergoing hormone-replacement therapy. It is possible that after prolonged estrogen-deprivation the body loses the capacity to respond to estrogen. Such a finding would emphasize the importance of early hormone-replacement intervention so that women can benefit from the positive effects of maintained estrogen levels.

B) What is the effect of testosterone on BDNF gene regulation? Do testosterone and exercise interact to regulate BDNF? In males, testosterone is converted to estrogens, and the beneficial effects of testosterone on cognitive function and health are thought to be mediated through the effects of estrogen.

7) Additional background information:

As most people are now aware, several recent studies have shown that estrogen-replacement can slow age-related cognitive decline and lower the risk of developing Alzheimer's disease. In addition, it has been known for several decades that physical activity and stimulation by one's environment can strongly influence the structure, chemistry, and function of the brain. In the past, estrogen and exercise have been considered to be 2 very separate themes. Here we show interactions between estrogen and exercise, that can affect both physical and mental health.



Robert and LaDorna Eichenberg

his past year, the Institute for Brain Aging received a personal check from Robert (Bob) and LaDorna Eichenberg. The Eichenbergs had previously contributed to the local Alzheimer's Association, but when they learned about the research going on at the Institute, they wanted to give a direct donation which could help to directly support research and free some of the Institute's scientists from spending time writing grants. We would like to take this opportunity to thank them for their generous donation and inspire our readers with a snapshot of their remarkable life story.

Bob and LaDorna met in school: night school at UC Irvine. Bob was taking a creative writing class on the GI bill back in 1974. LaDorna, a California native, had tried to enroll in the same class several times before, but it was always full. That year she decided that she was getting in no matter what. She went early and sat in, even though the class was again over enrolled. When the first student dropped the class, LaDorna got the next seat and met Bob. They've been married now for 26 years, each with several children from previous marriages.

The Eichenbergs didn't start out with much; but over the years, with hard work, sacrifice, and a bit of luck, they built their own successful company "Ellison Educational Equipment, Inc". Bob and LaDorna started Ellison in

DONOR SPOTLIGHT

1977 as a small idea in their 2-bedroom, 410 square foot apartment. Ellison has now grown to employ over 150 people and occupy a 132,000 square foot warehouse.

Ellison started with an idea of LaDorna's. While teaching art in the Tustin School district, she noticed a teacher cutting out 200 construction-paper shamrocks for a class project. The teacher's hands were bleeding and there were still 200 more shamrocks to cut. LaDorna thought a cookie cutter could do a better job and told her husband, Bob, her idea. Together, they co-invented and patented the "Ellison Letter Machine" and formed their small company.

Bob was an administrative aid to then California State senator James



The Eichenberg's showing their original Ellison Machine

Whetmore. Senator Whetmore had just retired, and Bob was unemployed. Bob spent two years developing

the concept, building prototypes, and selling the first machines while supported by LaDorna's teacher salary. When LaDorna lost her job to cutbacks in the arts, she joined Bob and took their machines to small trade shows up and down the California coast. When they demonstrated the Ellison Letter Machine at a single national teacher supply show, sales really took off. Today, Ellison employs international representatives, exhibits at more than 100 shows a year, and sells letter and art cutting machines to schools and craft centers. They even have their own website www.ellison.com. And the business has grown into a family affair. Not only is LaDorna's daughter the President of Ellison, but company policy is to celebrate each employee's birthday and provide a paid day off for employee's to get their US citizenship.

The Eichenbergs have never sought publicity for their charitable works. They agreed to allow us to tell their story in the hopes that it would motivate others who are well off to recognize their obligation to contribute to society in whatever way they can. Bob and LaDorna Eichenberg feel very fortunate and quoted Luke 12:48 as one reason they donated to the Institute for Brain Aging and Dementia. "For unto whomsoever much is given, of him shall be much required."



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In Memory of Charles "Ben" Sloan

"Kawas" Continued from Page 1

Her study on the use of anti-inflammatories has been a cornerstone in the field and provided much of the support for the hypothesis that brain inflammatory mechanisms are one of the key factors contributing to disease onset and progression.

Dr. Kawas also published the first prospective study that estrogen replacement therapy reduces the risk for developing Alzheimer's disease. The relative risk of AD in estrogen users as compared to non-users was a startling half, after adjusting for education, indicating a greatly reduced risk for woman who had reported the use the estrogen. These studies have provided important justification for various multi-center trials of anti-inflammatory and estrogen based treatments.





465 Walkers Join the BIG RED Team!

...to raise awareness and funds for the Alzheimer's Association of Orange County

An enormous "Thank You!" goes out to the hundreds of walkers who participated in the UCI Memory Walk Team in 2000! For the fifth consecutive year UCI had the most walkers and raised the most donations for a non-profit organization! The UCI Big Red



Team raised more than \$16,000 in funds that will benefit the local Alzheimer's Association that offers free services to patients and families in Orange County. More than 6,000 walkers participated and total raised funds exceeded \$418,000!!!





2001 Family Education Series

Featuring: Cordula Dick-Muehlke, Ph.D.

February 13 Alzheimer's Disease, Lewy Body, FTD:

Differences in Symptoms & Care

June 12 Communicating with Patients

September 11 Early Stage Issues

December 4 How to be a Healthy Caregiver

Workshops are free of charge, but seating is limited so please R.S.V.P. at 949-824-2382. All lectures will take place at the University Club on the UCI campus from 5:00-6:30pm. Beat the traffic and join us for refreshments from 4:30-5:00pm.

Concerned about Memory
Loss for yourself
or a loved one?

Please call us for information on specialized assessment and treatment services (949)824-2382 or visit our website at:

www.ad.uci.edu.



Alzheimer's Disease Research
Center of California
at the
UCI Institute for Brain Aging & Dementia
1100 Gottschalk Medical Plaza
Irvine, CA 92697-4285

For information and appointments, please call: 949-824-2382

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C A L E N D A R 2001

Feb. 13
Workshop:
Differences in
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May 11 Annual Research Conference

June 12
Workshop:
Communicating
with Patients



Sept. 11Workshop:
Early Stage Issues

October 6
Memory Walk
at Irvine Spectrum

Dec. 4
Workshop:
How to be a
Healthy Caregiver

"The Orchard", by Sarah

Artwork borrowed from 2001 Orange County Alzheimer's Association "Memories in the Making" Calendar. The Calendar may be purchased by calling (714) 283-1111.

To Register, Please Call 714-283-1111.

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Alzheimer's Disease Research: Diagnostic Subtypes, New Treatments, and Hope for Prevention

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