Volume 4, Issue 1

Institute for Brain Aging & Dementia

Brain Aging Bulletin

University of California, Irvine

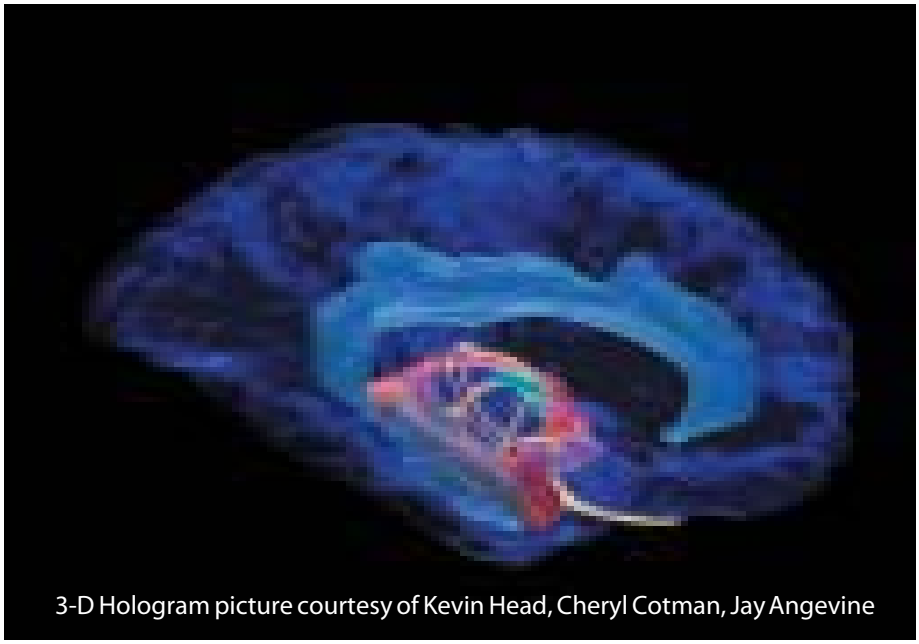
SPRING 2002

CONTENTS

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

Hologram: Unveiling the Secrets of the Limbic System

Alzheimer's disease preferentially attacks structures in the brain known as the limbic system. The highlight of the Institute's Annual Holiday membership reception last December was an innovative presentation of the "Limbic System Hologram," a project developed jointly by Cheryl Cotman, Jay Angevine, and Kevin Head. Cheryl is an art student at the California Institute for the Arts; Jay is Professor Emeritus of Cell Biology and Anatomy at the University of Arizona, and Kevin is a computer programmer and specialist. The limbic system of the brain is one area that is targeted early in the progression of Alzheimer's disease. The presentation included a 3-D computer reconstruction/animation of the complex nerve centers and connections of this brain subsystem, plus the unveiling of a hologram of the system, as a grandfinale, all in color.



3-D Hologram picture courtesy of Kevin Head, Cheryl Cotman, Jay Angevine

The design and building of the computer animation production and the hologram proved to be tedious and difficult projects. Initial stages included many drawings by Cheryl using neuroanatomy texts, monographs, and illustrations of dissections to capture the system in oblique perspective. Much to the team's surprise, there was wide variation found among the many sources in shapes and connections of the components that

"Hologram" Continued on Page 5

UCI Institute for Brain Aging & Dementia

The Progress and Accomplishments of the Institute: A 5-Year Review

The Institute for Brain Aging and Dementia was established, after competitive review, in March of 1995 as an Organized Research Unit (ORU) within the University of California system. The goal of the Institute for Brain Aging and Dementia is to discover the principles for aging successfully and improving cognitive and behavioral functions for those with functional loss. This task requires a multi-disciplinary research approach. The Institute, directed by Dr. Carl Cotman, seeks to facilitate the efforts of faculty and students in brain aging research through the creation and support of common facilities, development of joint grants and scholarly group interactions. This designation as an ORU requires that the Institute undergo a comprehensive review by external peers every five years. Thus, the Institute underwent the required external review process in early June of 2001.

The review team was comprised of three esteemed colleagues from outside of the university and three inside reviewers who were external to the Institute. Two days were devoted to a detailed agenda, in which the reviewers met sequentially with small groups within the Institute, from undergraduate and graduate students to basic scientists and clinicians, from staff to faculty. The outcome of the review was an overwhelming success, and the Institute was awarded five more years of support from the University of California. Notable comments from the reviewers include:

- The Institute has expanded and continues to stay at the forefront of research in aging and dementia.
- Clinical research is in a growth phase with the Institute, which is poised to make other important contributions in clinical care of the aged.
- Overall research quality is outstanding, with international visibility.
- The Institute's intellectual milieu is one in which clinicians and scientists complement one another to create synergistic investigations.
- The Institute has an outstanding funding record that largely is reflective of its ability to enhance collaborative interactions, and to identify and capitalize on new opportunities.

In response to the detailed and considerate review by the outside reviewers, the university has given another five years of support to the Institute, added an additional administrative support position, and has applauded the work of the Institute.

Specialized Educational Support Groups for FTD & Lewy Body Dementia Cargivers

We welcome all caregivers of patients with Frontal Temporal Dementia (e.g., Pick's Disease and Primary Progressive Aphasia) and Lewy Body Dementia to our monthly support groups.

When? Meetings are held the first Wednesday of each month from 9:30am-11:30am

Where? Meetings are held in the 1st floor conference room of the Gillespie Neuroscience Research Facility on the UCI Campus.

Co-Facilitators are Lynne Conger of the Alzheimer's Association and Shirley Sriyordsa of the UCI Institute for Brain Aging & Dementia. For more information about the group, please call (949) 824-8135

Alzheimer's Disease Research Center of California

at the
UCI Institute for Brain Aging & Dementia
1100 Gottschalk Medical Plaza
Irvine, CA 92697-4285
website: www.alz.uci.edu
For information and appointments please call: (949) 824-2382

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Clinical Coordinator
Allison Gay
Research Associate

UCI Institute for Brain Aging & Dementia

New Research Project: The 90-Plus Study

For centuries, explorers have been searching for the fountain of youth. Today, researchers are seeking the keys to "successful aging" and studying the cognitive and brain characteristics that are associated with healthy aging. People over the age of 90 are the fastest growing segment of the population. Studies are being conducted to obtain information to ensure quality, and not just quantity of life for people as they age. A new project for the Institute for Brain Aging and Dementia at the University of California, Irvine is a study of the oldest old. UCI will be recruiting individuals 90 years of age and over into the 90-Plus Study. The 90-Plus Study will examine the relationship between cognitive abilities, or thinking skills, and brain tissue in people over 90 years of age. Researchers will be examining lifestyle, health, and genes of those who participate. Volunteers for this study will have visits scheduled at the new Clinic for Aging Research & Education, directed by Claudia Kawas, M.D., located in the heart of Laguna Woods at the new Town Centre complex. Arrangements can be made for some frail individuals to be seen in their homes. People over the age of 90 or their family members who are interested in learning more about the 90-Plus Study should call the Clinic for Aging Research and Education.

University of California, Irvine
Institute for Brain Aging and Dementia

Clinic for Aging Research & Education

23461 El Toro Road, Ste. 150
Laguna Woods, CA 92653
(949) 824-9121
email: clinicalresearch @alz.uci.edu

Register Today!

2002 Annual Alzheimer's Disease Research Conference

Alzheimer's Disease: New Approaches to the Cure

May 10, 2002

Topics will Include:

- The Role of Stem Cells in Neurodegeneration Disorders
- Neuronuclear Imaging of Early Alzheimer's Related Changes in the Human Brain
- Clinical Trial Update: What's on the Horizon?
- Mental and Physical Activity and Alzheimer's Risk
- Optimizing Brain Function with Age
- Gene Therapy for Alzheimer's Disease

Featured Speakers:

James Fallon, Ph.D. • Daniel Silverman, M.D., Ph.D. • Leon Thal, M.D. • Robert Friedland, M.D. • Claudia Kawas, M.D. • Carl Cotman, Ph.D. • Mark Tuszynski, M.D., Ph.D.

Hosted by:

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

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

UCI Institute for Brain Aging & Dementia

Gene Chip Micro Array Technology

Victoria Perreau, Liqi Tong, Hong Shen, Anna Parachikova and Carl Cotman

What is a DNA Micro Array?

Modern technology now allows scientists to examine all the genes in the brain in a single experiment. This dramatically changes how researchers can search for genes, which may be important in disease processes. The technique that allows scientists to make a fingerprint of all the brain's genes is called a DNA Micro Array. A DNA micro array is a miniature array of DNA sequences bound to a matrix, usually glass. Each DNA sequence corresponds to a fragment of a single gene and many thousands of these spots can be arrayed in an area the size of a postage stamp.

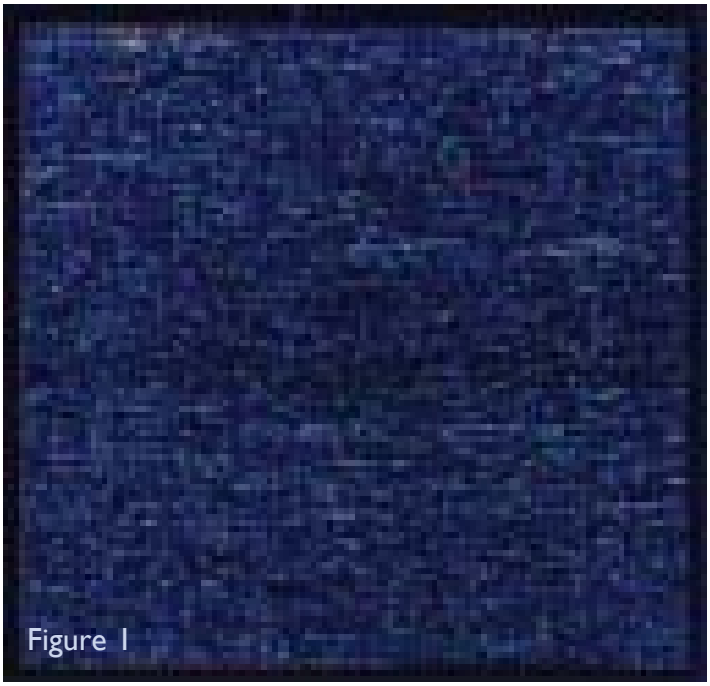


Figure 1

What is RNA?

Almost every cell in an organism has a nucleus containing the DNA encoding a copy of every gene in the genome. The specific genes expressed in a cell determines what cell type it will be and how it will function. When genes are expressed they are transcribed into RNA in the nucleus. The RNA is then transported out of the nucleus and translated into proteins.

How is a DNA micro array used to determine gene expression?

RNA is extracted from cells or tissue of interest and labeled with a fluorescent dye. This labeled sample is applied to the Micro Array and the RNA reacts with its corresponding DNA printed on the array and becomes bound to it. Unreacted labeled sample is washed off and the array is read with a scanning laser and high-speed fluorescent detectors. Where labeled RNA has bound to the array, light is emitted. The intensity of each spot is quantified and its location determined, thus identifying which corresponding gene fragment reacted with the labeled RNA. Only those genes, which were expressed in the tissue sample, will react with the labeled RNA. Thousands of genes can be represented on each Micro Array, so expression data for thousands of genes can be collected in a single experiment. Computer programs are utilized to 'mine' the data to identify patterns in gene expression that may be important for disease processes or in improving health. A sample of a Micro Array showing the gene expression pattern of the brain is shown in figure 1. Each spot corresponds to a single gene, and the ones that are expressed in the sample are shown in red.

How is the Institute using Micro Arrays to understand aging and disease?

The Human Genome project has identified that there are approximately 30,000 genes in the human genome. However the function of only a few of these is currently known. Conventionally, to identify gene expression changes in disease states, single genes were analyzed one at a time, and these genes were chosen from their known properties. Unknown genes with importance in disease are rarely identified using conventional techniques. DNA micro array technology allows the expression patterns of thousands of genes with unknown function to be examined. It's like looking for a needle in a haystack with thousands of large magnets!

"Gene Chip" Continued on Page 8

"Hologram" Continued from Page 1

comprise the limbic system - in fact, no two sources were alike. At one point, the designers even built a model with lumps of clay for the centers, pipe cleaners for the connections, and picture frame wire and brads for support. Following this, Cheryl and Jay resorted to material prepared by 19th century methods: thin slices (35 microns) of the entire brain, cut and stored in order, stained to show its major tracts and thereby the size and shape of its every part. Some 2000 of these sections were studied. Using high-resolution color photographs of them and tracing paper, Jay traced and color-coded each connection and center of the system in 120 sections, 70 of which were used in the final product.

When Kevin added his skills in computer-generated technologies to the art and science skills of Cheryl and Jay, the team was complete! Using Surfdriver and 3-D Studio Max, he digitized Jay's tracings to accurately reconstruct the system. This work is also taxing: pencil tracings are made with smooth continuous lines, but digitizing involves separate entry of points along those lines. Surprising departures from accepted shapes of structures, as well as finer details, turned up. Cheryl and Kevin took these in stride, but Jay's deep-seated anatomical prejudices had to be unseated, with the advice "What you see now is the way it really is!"

Near the end of the presentation, the model was set in motion, allowing the 200 people present to view the circuitry of this mysterious system tumbling in space and to ponder its roles in many of our everyday global functions: learning, spatial memory, emotion, sexual behavior; its malfunctions in neurological and psychiatric diseases: depression, bipolar disorder, schizophrenia, and Alzheimer's disease. Further advancement of the computer animation demonstrated the standard progression of Alzheimer's disease.

The team — artist, anatomist, computer specialist — hopes that their work provides a template, a new kind of map, for charting functional circuits and disease patterns in the brain and a model of how a multi-disciplinary approach is well suited to the study of the hypercomplex problems the brain presents.

2002 Family Education Series
Upcoming Workshops

June 11	**Insights into Early Stage Dementia**
July 31	**A Caregiver's Workshop: Creating a Partnership With Your Doctor When the Diagnosis is Alzheimer's Disease or a Related Illness**
September 10	**Strategies to Reduce Behavioral Symptoms in Dementia**
December 10	**Legal and Financial Planning: Talk to the Experts**

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. If you're not already on our mailing list, let us know!

UCI Institute for Brain Aging & Dementia

Dietary Antioxidants Improve Learning Ability in Canines

E. Head, N.W. Milgram, B.A. Muggenburg, S.C. Zicker and C.W. Cotman

Institute for Brain Aging & Dementia, UCI; Division of Life Sciences, University of Toronto, Canada;
Lovelace Respiratory Research Institute, Albuquerque, NM; Science & Technology Center, Hill's Pet Nutrition, Inc. Topeka, KS.

The use of antioxidants, such as Vitamins E and C, is associated with a reduced risk for developing Alzheimer's disease in epidemiological studies. However, the number of clinical studies determining whether antioxidants improve cognitive function in patients with Alzheimer's disease is quite limited. More information is available from studies in aged rats in which providing animals with blueberry and/or strawberry extracts can improve learning ability. We hypothesized that this nutritional strategy of enriching diet may lead to significant improvements in cognitive function in aged dogs.

Why study aged dogs?

Aged dogs naturally develop senile plaques in the brain that are similar to those seen in the human brain during normal aging and in mild Alzheimer's disease. In addition, some aged dogs can learn and remember as well as young dogs (successful aging), whereas others develop severe cognitive impairments (pathological aging). Thus, identifying interventions that improve cognition in aged dogs may be helpful for designing future clinical trials to prevent or reduce cognitive dysfunction in Alzheimer's disease.

How are we conducting the study?

To evaluate whether antioxidants may be a promising intervention for reducing cognitive impairments, we have been studying a group of 48 aged dogs and 17 young dogs for a period of 3 years. Animals have been placed into 1 of 4 treatment groups:

* No intervention to serve as age-matched controls (CTL-normal senior canine diet)

* Antioxidant enriched diet (senior canine diet enriched with vitamins E and C, alpha-lipoic acid, l-carnitine, and fruits and vegetables)(AOX)

The antioxidant diet was developed in collaboration with Hill's Pet Nutrition. Every year, the learning ability of our animals is re-tested with dogs being rewarded with food when making the correct response.

Aged dogs receiving the antioxidant diet show cognitive improvements

The dogs receiving the antioxidant diet are showing significant improvements in learning ability. On one task, called landmark discrimination, we show dogs two identical objects (red wooden blocks) with a "landmark"(yellow wooden cylinder) indicating where the food reward is hidden. The dogs must learn to look for the landmark and decide which of the two identical objects is closest to the landmark object in order to find the food reward, see Figure 1. Aged dogs on the antioxidant diet make fewer errors, approximately a 43% improvement, during learning, refer to figure 2.

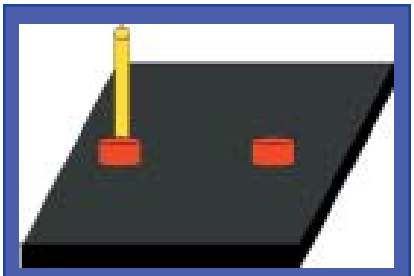


Figure 1

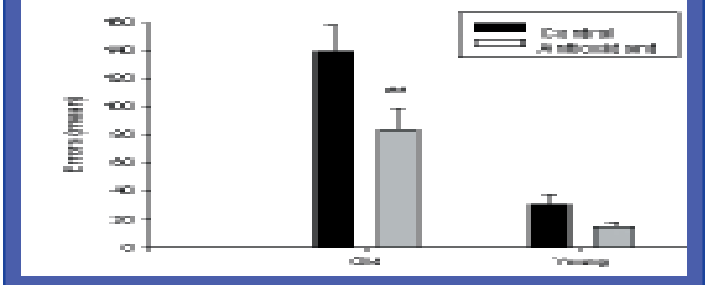


Figure 2

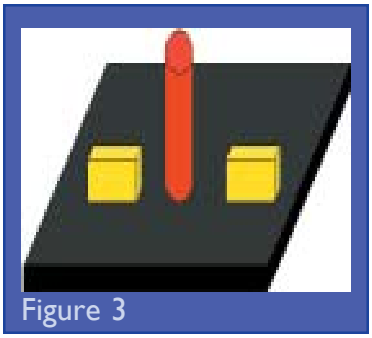


Figure 3

On a second problem, called oddity discrimination, dogs are shown three objects. Two of these objects are identical and the third is different. The correct answer is to pick the object that is "different.", refer to

Figure 3. We can make the problem more difficult by choosing objects that look more and more similar. Animals being fed the antioxidant diet show between 31-58% improvements in error scores when solving these problems when compared to animals receiving the normal diet, refer to figure 4.

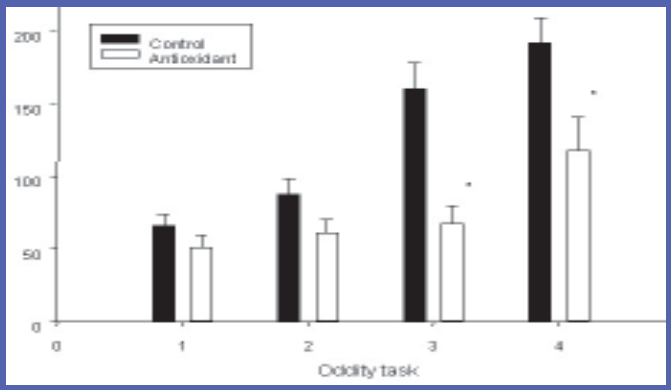


Figure 4

Why are these results new and interesting?

This is the first report of a dietary intervention showing dramatic improvements in cognitive function in a higher mammal. Most studies to date have been in rodent models and there is good evidence to suggest that the way rodents metabolize nutrients is significantly different from how we as humans, derive nutrients from our diet. On the other hand, dogs have very similar nutritional requirements and metabolize food in a consistent manner with humans. Thus, finding such unexpectedly large cognitive improvements with a relatively simple treatment is very exciting and can be more directly translated to the clinic than studies conducted in rodents. It is also exciting to note that this same diet is now commercially available through your veterinarian for management of behavioral problems in elderly pet dogs (Hill's Prescription Diet Canine b/d, Hill's Pet Nutrition, Inc.). Thus, these studies have proven beneficial both for our companion animals and in the future, we hope, for patients with Alzheimer's disease.

What is the next step in our research?

We have one more year of the study to complete and are currently analyzing the results of our magnetic resonance imaging (MRI) scans that are being conducted by Dr. Lydia Su at the Department of Radiology here at UCI. We have included MRI scans because they provide a noninvasive method to monitor the effects of the diet on brain function. We anticipate that these results will be available in the near future. In addition, another part of the experimental design in the current study was to include an environmental enrichment condition where animals are given additional physical exercise and problem solving experience. The results of this phase of the study will also be completed in the near future.

New Staff at the Institute

Rosa Goette and Ken Krisnasmit

Recently, the Institute for Brain Aging and Dementia has had two new additions in the front office of the Alzheimer's Clinic at the Gottschalk Medical Plaza. Some of you may have already had the opportunity to meet or talk to our newest staff members, Rosa Goette and Switaya "Ken" Krisnasmit.

Many of you may recognize Rosa as a familiar face from the Gottschalk Medical Plaza. As the new Program Assistant at the clinic, you may hear her friendly voice on the phones helping to schedule appointments.

Ken, who is a graduate from UCI, is the new patient care coordinator with the Alzheimer's Clinic and is actively involved with patients and families going through the assessment process.

For more information on the program or to make an appointment at the UCI Alzheimer's Clinic call (949) 824-2382.

Clinical Trials Update

Institute for Brain Aging and Dementia
University of California, Irvine
Current Clinical Trials Options

Estrogen Prevention Study

- Double-blind 4-year study of estrogen to evaluate for prevention of dementia
- For normal women only who are ≥ 65 years old with a family history of dementia
- Cannot be currently taking hormone therapy

Prevention Instrument Study

- Paper and pencil instrument study to help us develop new tests for future dementia prevention trials; not a treatment study
- For normal men and women ≥ 75 years old
- A small fee is paid at each visit for participation in this study

For more information on clinical trials at the center, send us an email or contact the clinical trial staff.

Depression and Alzheimer's Disease

- Follow-up study for individuals with Alzheimer's disease with and without depression; not a treatment study
- For men and women who have Alzheimer's disease
- A small fee is paid at each visit for participation in this study
- This study will begin in May of 2002

Antioxidant Toxicity Study

- Double-blind 6-month study of three different antioxidants in combination
- For normal men and women ≥ 75 years old
- This study will begin in May of 2002

Ampakine Treatment Study

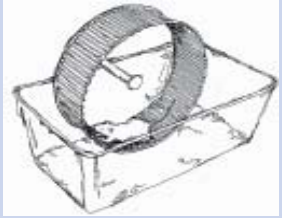
- Double-blind 14-week study of a new compound (ampakine) that may inhance memory
- For men and women ≥ 60 years old, who have a mild cognitive impairment
- This study will begin in May of 2002

Email: clinicaltrials@alz.uci.edu
Phone: Catherine Ortiz at (949) 824-8726 or Hyunmie Kim at (949) 824-8136.

"Gene Chip" Continued from Page 4

The Institute is devoted to understanding disease and aging processes in the brain and we have been utilizing this technology to identify new genes of interest. Utilizing tissue from the Repository we are investigating the differences in gene expression patterns in the brains of Alzheimer's disease patients at different stages compared with healthy aged brain donors. We hope to generate a more complete map of the disease process and identify novel genes involved in the early stages of the disease, which may suggest new treatment directions.

There is increasing evidence that physical activity benefits cognitive function and this is another important research project in the lab. Rats and mice are used to investigate the effects of exercise on gene expression in the brain. Animals, housed with running wheels in their cages, voluntarily run about eight miles each night. We have shown voluntary exercise in rats modulates the expression of many different types of genes in the hippocampus (Tong, et al 2001), including those involved in plasticity. We are currently researching the effects of exercise in aged mice.



Artwork by Cheryl Cotman

For further information you can visit:

The Human Genome project
http://www.ornl.gov/hgmis/project/about.html

Unity in the midst of Tragedy: 2001 Memory Walk

Despite the challenges the nation faced on 9/11, Orange County showed unity in the fight against Alzheimer's Disease

"Proud in Purple," the UCI Memory Walk Team recruited over 420 walkers!

After the nation was struck by tragedy on September 11, 2001 Orange County demonstrated unity in raising awareness and funds for the Alzheimer's Association of Orange County at the 2001 Memory Walk. The Orange County Memory Walk attracted the largest number of walkers in the nation and raised nearly half a million dollars. A special thank you goes out to the hundreds of walkers and "forget-me-nots" who participated in the UCI Memory Walk Team 2001! For the 6th consecutive year, the UCI Team was awarded 1st place for the "Largest Team" and received 2nd place for raising the most donations as a non-profit organization. Co-Captains Shirley Sriyordsa (UCI Institute for Brain Aging), Elizabeth Eastin (Alzheimer's Association of O.C.), Dr. Diane Edwards (Professor at the Saddleback College Emeritus Institute), and Milly Polash (resident of Laguna Woods) recruited over 420 walkers and raised over $10,000 in funds that will aid families through the local Alzheimer's Association.

Save the Date!
Join us for the
2002 Memory Walk
October 5, 2002
at the Irvine Spectrum.
To receive information about the walk or joining the UCI team, call (949) 824-2382.

Brain Aging

UCI Institute for Brain Aging & Dementia

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In Honor of Joyce Tucker
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1.) Checks should be made payable to: ***UCI Foundation*** *and in the Memo section please write:* ***Alzheimer's Research***

2.) If the donation is being made in memory/honor of someone, please include a note with information as to where the acknowledgements should be sent to.

3.) Please mail the donations to:
Institute for Brain Aging & Dementia
1113 Gillespie Neuroscience Research Facility
Irvine, CA 92697-4540

To make a donation to the UCI Institute for Brain Aging, log on to:
http://www.alz.uci.edu/donate.html
or call (949) 824-8135.

UCI Institute for Brain Aging & Dementia

C A L E N D A R 2002

May 10
Annual Research Conference
Alzheimer's Disease: New Approaches to the Cure

June 11
Family Educational Series Workshop
Insights into Early Stage Dementia

July 31
Family Educational Series Workshop
Creating a Partnership with Your Doctor when the Diagnosis is Alzheimer's Disease or a Related Illness

September 10
Family Educational Series Workshop
Strategies to Reduce Behavioral Symptoms in Dementia

October 5
Annual Memory Walk at the Irvine Spectrum. Help the cause, join the team!

December 10
Family Educational Series Workshop
Legal and Financial Planning: Talk to the Experts

"Lighthouse" by Bernyl

Artwork borrowed from 2002 Orange County Alzheimer's Association "Memories in the Making" Calendar. The Calendar may be purchased by calling (714) 283-1111.

Save the Date:
Alzheimer's Disease:
New Approaches
to the Cure

A Day-Long Conference
Friday, May 10, 2002
For More Information
or To Register,
Please Call 714-283-1111

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