Estrogen Trial Results are in!

An accumulation of research over the past twenty years suggested that estrogen might play a beneficial role with respect to Alzheimer’s disease. Many of these studies were done in the basic science laboratory, demonstrating repeatedly that estrogen had many beneficial effects on brain cells and function. And, several population-based surveys had suggested that post-menopausal women on estrogen replacement therapy had a greatly reduced risk of developing the disease. In addition, several small clinical trials on Alzheimer’s patients had suggested that estrogen replacement therapy could be of benefit once the disease begins. However, these clinical studies were very small in size and of short-duration, generally ranging from six to eight weeks. It was, therefore, very important to conduct a larger study over a longer period of time to truly discover the role that estrogen can play in the treatment of Alzheimer’s disease.

Over the last several years, Drs. Ruth Mulnard and Carl Cotman and other investigators at various universities around the nation began a study to rigorously evaluate the efficacy of estrogen in AD patients. This study was a definitive, placebo-controlled, double-blind, randomized clinical trial of one year duration involving women with mild to moderate Alzheimer’s disease.

(Continued on Pg. 3)

Vaccine for Alzheimer’s Disease?

Recently an exciting paper was published in Nature (1999;400:173-177, “Immunization with amyloid delays Alzheimer-disease-like pathology in the PDAPP mouse” by Dale Schenk and associates, Elan Pharmaceuticals, 800 Gateway Blvd., South San Francisco, CA 94080) showing that immunization of a transgenic mouse model of Alzheimer’s disease (AD) with β-amyloid almost eliminates the development of AD-like pathology. β-Amyloid is a small molecule of 42 amino acids that accumulates in the brain of Alzheimer’s patients. It is believed to be one of the factors causing dementia. Originally, discovered by Alzheimer in 1907, β-amyloid is one of the hallmark signatures of the disease. Very little, however, has been discovered on how to prevent its accumulation or eliminate it once it has formed. This paper is one of the first major leads showing that simple immunization with amyloid may be a promising new therapeutic approach.

(Continued on Pg.2)
approach.

The role of the immune system had already been implicated because the use of anti-inflammatory drugs (NSAIDS) delay AD onset. In this new study, a transgenic mouse model of AD was used that overexpresses the precursor molecule that makes amyloid, called the amyloid precursor protein. This protein, when cleaved, generates the molecule amyloid which, over time, deposits within the brain. These animals are called transgenic because they have been engineered to incorporate a new or foreign gene (transgene) within their own cells. In this case, the foreign gene was the human form of the amyloid precursor protein with the Swedish mutation. The Swedish mutation is known to accelerate the development of amyloid and, therefore, the transgenic mouse is a good experimental approach and an appropriate model.

The investigators injected small quantities of amyloid into the mice beginning at 3 months of age and then measured the build-up of amyloid over the next 11 months in immunized vs. control mice. The injection tricked the mouse immune system to recognize and attack the amyloid plaque. The results were startling! The mice that had been immunized showed virtually no accumulation of amyloid. Typically a few percent of the total brain will consist of amyloid deposits, and in this case, the levels were barely detectible if at all. This result is exciting but does not address the question that once the amyloid is deposited, can it also be removed. To do this, the investigators injected mice during the early stages of amyloid formation (11 months) and then studied them several months later. Again, the results were quite impressive. The old mice showed less accumulation of amyloid, and in fact, it was nearly removed. It did not continue to build up. There were small deposits occasionally which were surrounded by activated immune cells called microglia, otherwise, the brains appeared to be normal.

So, what are the next steps? First, obviously, this is research on mice and this does not show that the approach will work on humans. There are other concerns. Autoimmunity (over-reaction to self) is one concern. The mouse has the human gene and the immune reaction may have spared the natural mouse protein. The immune response could have selectively been against the human gene product as opposed to the mouse (and avoided autoimmunity). In humans, of course, there is no foreign gene, and thus, it is possible that the immune system may develop a different type of reaction to immunization with amyloid. This, and several factors, will require study in animal models, including other animal models such as primates, and eventually, very careful feasibility studies in a small group of patients. It is clear that there are several other differences in the mouse model relative to the human. For example, UCI investigators David Cribbs and Andrea Tenner have recently shown that the mouse immune system is less reactive to amyloid than is the human immune system. Investigators, though, are cautiously optimistic and excited about this new lead. As Carl Cotman, Director of the Institute for Brain Aging and Dementia, said, “This is an exciting, fundamental breakthrough that gives us all a new opportunity to prevent the build-up of amyloid in the human brain. While a small amount of immunity is probably good, on the other hand, too much will be too much of a good thing and probably produce negative effects. We’ll just have to see.” It must be noted, however, that amyloid is only one of the problems that develops. While it is believed to be a primary reason for much of the pathology that develops, there is still debate and it is possible that other aspects such as the accumulation of tangles will still prevail. The rate of advance will depend on the research dollars available. Investigators at UCI and elsewhere are actively studying the role of immune responses in the disease. It clearly plays an important role in the disease process and this reinforces careful control immune responses as a key therapeutic approach.
results were published this year in the February 23rd issue of JAMA. (This study selected unopposed estrogens because of previous investigations that progesterone may mitigate some of estrogen’s beneficial effects in the central nervous system.) The study enrolled 120 women who were randomized to receive a single dose of placebo, Premarin .625 mg or Premarin 1.25 mg. The three groups were assessed at the beginning of the trial and at a number of intervals throughout the course of the twelve months. This study was conducted at 32 sites across the nation, and was conducted with members of the Alzheimer’s Disease Cooperative Study unit (a consortium of Alzheimer’s Centers supported by the National Institute on Aging).

The conclusion was quite definitive: estrogen replacement therapy for one year did not slow disease progression nor did it improve global, cognitive or functional outcomes in women with mild to moderate Alzheimer’s disease. Thus, the study does not support the role of estrogen for the treatment of this disease.

This does not mean, however, that estrogen replacement therapy is not important to prevent the development of Alzheimer’s disease. Several controlled clinical studies are now under way to rigorously evaluate the potential role of estrogen in the prevention of Alzheimer’s disease. The bulk of current evidence indicates that some usage of estrogen post-menopause will be of benefit to women.

Interestingly, the results of the estrogen study are similar to other studies in cardiovascular disease where estrogen appears to reduce the probability of developing chronic heart disease, but once the disease starts, it is of less benefit, if any benefit, in reducing the rate of decline or the improvement of symptoms. As Dr. Mulnard said, “I was shocked when I heard the results because we had fully expected there to be a benefit for mild to moderate Alzheimer’s patients. However, the results are quite clear and the great value of research is that one discovery leads to new ways to think about the disease and it’s management.” The reports of this research were televised nationally on CNN and through various other media across the radio and newspapers. We are proud of and wish to thank all those that participated in the study.

Full Text of the article titled “Estrogen Replacement Therapy for Treatment of Mild to Moderate Alzheimer Disease: A Randomized Controlled Trial” can be found in the Journal of the American Medical Association, February 23, 2000, V. 283, No. 8, pp. 1007-1015, Ruth A. Mulnard, R.N., D.N.Sc., Carl W. Cotman, Ph.D., Claudia Kawas, M.D., et al., or at their website: http://jama.ama-assn.org/issues/v283n8/full/joc91949.html

Did You Know?

The Institute for Brain Aging & Dementia will gladly arrange a tour of their research facilities at the Gillespie Neurosciences Building on the UCI campus. Tours provide a glimpse of the activities performed by researchers at the basic science level. Tours are conducted once a month. Interested parties may contact Elizabeth Eastin at 949-824-8135 for specific dates and times.
The Institute is pleased to announce the generous donation of a Gift Annuity from Mr. Corbin Hewitt. In July, Mr. Hewitt visited the Institute for Brain Aging’s research lab and decided to donate his entire estate to support the Institute’s research into the causes and treatments for neurodegenerative disease, including Alzheimer’s and Parkinson disease.

Mr. Hewitt was born in 1912 in the small mining town of Lead, South Dakota. He grew up in Wyoming and still remembers “the bitter cold winter and frozen feet” of his youth. After graduating from high school, he served as a cook on a commercial ship that traveled between San Francisco and Australia, built sets in Hollywood and worked in construction all over the globe, including Saudi Arabia and Central America.

Mr. Hewitt served a four year stint in the Navy, helping construct runways and power plants on Midway Island prior to the war. He returned to the US aboard a repair ship that was later destroyed at Pearl Harbor - while tied to the battleship Arizona. He was re-called by the Navy and assigned to a destroyer, but his construction skills got him transferred to help rebuild Pearl Harbor. The destroyer he was assigned to sank with all hands in the battle for Okinawa. While working in Hawaii, he caught a severe cold and was hospitalized. His mother sent him vitamin E to restore his strength. He says that he’s taken vitamin E daily ever since and has never been sick again.

Mr. Hewitt lives on his own and still drives, although he “avoids the freeways”. He remains very active, swimming every day and dancing three times a week. He advises younger people to “work till you drop; and then keep working” and also to “avoid fried food”. He attributes his vitality to a lifelong habit of vigorous exercise and anti-oxidant vitamins. After learning about Gift Annuities at a lecture, he decided he “wanted to donate to older people”, and contacted the Institute for Brain Aging.
Clinical Trials Update

Currently Enrolling Trials

**Melatonin Trial:** We have been enrolling subjects in a new study that is recruiting subjects with sleep disturbances as part of their Alzheimer’s disease. The study will test the ability of **Melatonin** to improve sleep patterns in these patients over a thirteen-week period.

**Mild Cognitive Impairment (MCI) Trial:** We are currently recruiting for a three year dementia prevention trial targeted at persons with mild cognitive impairment (isolated memory problem, but not yet Alzheimer’s disease), in which **Aricept and Vitamin E** will be used to try to prevent the occurrence of dementia in these subjects.

**For Control Subjects Only: MCI Instrument Protocol:** In conjunction with the “Mild Cognitive Impairment (MCI)” trial, we will be testing some of the paper and pencil tests from that trial on normal control subjects. This trial will give us normative data on these measures for comparison with the data from the patients with Mild Cognitive Impairment.

**Olanzapine Trial for Treatment of Psychosis Symptoms:** Successful treatment of the psychosis symptoms (e.g., hallucinations, delusions) that may be associated with Alzheimer’s disease is the next problem under research. In collaboration with Eli Lilly and Company, we will be testing the ability of **Olanzapine** to treat these psychosis symptoms. Olanzapine is currently FDA-approved for the treatment of schizophrenia, but not yet available for the treatment of AD.

**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.

**Non-Steroidal Trial:** We are currently recruiting for a 14 month trial to determine whether treatment with Vioxx or Naproxen for one year will slow the rate of decline of cognitive function and clinical deterioration in patients with Alzheimer’s disease. This trial is an effort to find a useful anti-inflammatory regimen for patients with AD.

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.

(Donors Continued from Pg. 4)

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Mickey Roberts
Donald & Betty Jean Robbins
Mr. & Mrs. Edmund Santellano
Mitchell & Patricia Swieca
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In Honor of Mr. & Mrs. Earl Rosenstein’s 50th Wedding Anniversary
Arthur & Rochelle Shapiro

In Memory of Lester Samstag
Mrs. Lester Samstag
Cheryl Samstag

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In Memory of Cecil E. Wallis
George & Anna Johnson
Jan & Leon Madnick
Robert & Leigh Wilson

In Memory of Jennie Williams
Diane M. Martin
Hats off to the 376 UCI Walkers who participated in the 1999 Memory Walk at the Irvine Spectrum!

The UCI Team raised more than $10,000 in registrations and donations. Two more plaques have been added to the collection! For the fourth year in a row, UCI was named the “Largest Team Overall” and this year we were surprised to learn that we were also the “Organization that Raised the Most Donations”!

Special thanks to three additional team leaders who volunteered their services for this year’s cause: Milly Polash from Laguna Woods, Leisure World, Susan Hirasa from the Department of Geriatrics at UCI and Shirley Srijordsa a new full time staff member at the Alzheimer’s Clinic. We would not have reached our goals with out their support and commitment.

Over $300,000 was raised by the event and more than 6000 walkers attended. Money raised from the event will go directly to the patient & family services that are provided free of charge by the Orange County Alzheimer’s Association. If you would like more information regarding this event or services provided by the Alzheimer’s Association, please call 714-283-1111.
UCI Team Roster
Walkers, Ghosts & Sponsors

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Herbert Acker
Irma Acker
Jack Allen
Ruth Allen
Connie Anderson
Aileen Anderson
Ellen Antel
Eloria, Corey, & Mark
Armstrong
Donna Augustine
Mike Augustine
Jeanne Bader
Ruth Bailey
Clara Baker
Eileen Barret
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Sylvia Beitscher
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Sylva Bergthold
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Adeline Zheutlin
Catherine Zimmermann
Miriam Zolten-Fleisher
Ruth Zucker

Acceptance from the Institute would have been even more meaningful if it weren’t for the fact that my grandmother had Alzheimer’s disease. It was the last thing she would have wanted. But the Institute’s work has helped to advance our understanding of the disease and brought hope to those affected by it. That is why I decided to volunteer to help at the event. I want to do my part in supporting the mission of the Institute and helping to find a cure for Alzheimer’s disease.

I have always been passionate about supporting causes that are important to me. That is why I decided to volunteer to help at the event. The Institute’s work has helped to advance our understanding of the disease and brought hope to those affected by it. That is why I decided to volunteer to help at the event. I want to do my part in supporting the mission of the Institute and helping to find a cure for Alzheimer’s disease.
Adult Day Services of Orange County (ADSOC) in Huntington Beach has been expanding its services for persons in the early stages of Alzheimer’s disease and will continue to do so in 2000, with support from the Archstone Foundation. Although persons with Alzheimer’s disease and other forms of dementia are being diagnosed earlier, only a handful of services addressing the unique needs of these individuals are currently available in Orange County. Interestingly, 64% of the individuals diagnosed at the Institute for Brain Aging and Dementia during the last fiscal year were in the early stages of Alzheimer’s disease, as compared to 48% the prior year.

Two years of funding from the Archstone Foundation is making it possible for ADSOC to develop a continuum of services for the growing population of early stage individuals and their caregivers. In 1999, ADSOC developed a unique early stage day program with two levels or tiers. Tier One emphasizes preventative therapies (e.g., memory retraining classes) for persons in the earliest stages of Alzheimer’s disease, while Tier Two offers recreational outings for individuals who remain relatively independent but can no longer benefit from cognitive skills classes. This graduated program enables ADSOC to better meet the needs of individuals as they progress through the early stages of dementia. In 1999, early stage caregivers benefited from the “Living with Alzheimer’s Disease” psychoeducational series, a six-hour overview, which will continue to be offered periodically throughout 2000. A manual developed by ADSOC in 1999 now makes the latest information about early Alzheimer’s disease readily available to early stage individuals and their caregivers. Beginning to Make Sense: A Guidebook for Persons in the Early Stages of Alzheimer’s Disease and Their Caregivers, written by Cordula Dick-Muehlke, Ph.D., is available at no cost to families through ADSOC.

In 2000, ADSOC will use Archstone funding to broaden its range of early stage services. Many early stage individuals are involved in a variety of activities within the community and are not ready to give up an entire day to attend a program like the Adult Activities Center. ADSOC will begin offering 10-week sets of memory retraining classes for these individuals so they can learn techniques for enhancing their cognitive skills without enrolling in the day program. In addition, ADSOC will also start parallel support groups for early stage individuals and their caregivers, supplementing the early stage groups already being offered in North and South Orange County by the Alzheimer’s Association.

ADSOCS’s new services are designed to help early-stage individuals and their caregivers accept the diagnosis of Alzheimer’s disease and experience the benefits of peer support and therapeutic interventions.

For more information about the early stage services offered by ADSOC or to obtain a copy of ADSOC’s early stage guidebook, Beginning to Make Sense, contact Lynn Rodriguez, M.A., ADSOC Early Stage Care Manager, at (714) 593-9630.

New Support Group for Caregivers of Patients with Frontal Temporal Dementia
(e.g. Pick’s disease, Primary Progressive Aphasia)

An educational and support group for caregivers of patients with frontal temporal dementia began to meet in November 1999 and will meet monthly on the first Wednesday of each month on the UCI Campus. Co-facilitators are Kim Bailey of the Alzheimer’s Association of Orange County, Julene Johnson, Ph.D. 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.
New “Frontal Variant” of Alzheimer’s Disease

Most people are aware that Alzheimer’s disease (AD) is a degenerative brain disorder that is characterized by a progressive decline in cognition (i.e., thinking abilities). Alzheimer’s disease not only affects the ability to remember things, but also may affect an individual’s ability to carry on a conversation and even make decisions or good judgments. Both family members and researchers have noticed that not all patients with AD progress through Alzheimer’s disease in a similar way. This observation that patients with AD can behave in strikingly different ways led researchers to suggest that there are “subgroups” of patients who may experience the disease in a slightly different way than the typical patient with AD. These patients may have unique caregiving needs and may also provide clues about how the disease affects people differently. For example, some patients with AD have very early and severe impairments in their ability to talk.

Not all patients with AD progress in a similar way

and severe impairments in their ability to talk in addition to the typical memory problems. Other patients with AD also have early and severe impairments in their ability to solve visual problems. We usually think of Alzheimer’s disease as beginning with memory problems and then progressively involving more thinking abilities. But in the examples described above, some patients can experience more disruption to language or visual-spatial skills than usual. Very little research has been done to understand why some patients progress through the disease in a different manner than usual.

Recently at the Institute for Brain Aging and Dementia, researchers Julene Johnson, Elizabeth Head, Ronald Kim, Arnold Starr, and Carl Cotman identified a new “frontal variant” of Alzheimer’s disease in patients who have early and severe impairments on tests that measure the frontal cortex (front part of the brain). Many of the individuals with the frontal variant of AD may also have early and noticeable changes in behavior (such as impulsiveness, agitation, depression, etc.) that go along with difficulties in memory. Many family members have described such changes in their loved one. Studies to better understand the cognitive and behavioral changes associated with the frontal variant of AD are ongoing at the Institute.

The researchers also looked at the patterns of brain pathology in a group of patients who donated their brains to the brain autopsy program at the Institute for Brain Aging and Dementia. They found that the patients with the frontal variant of AD also had an increase in one type of pathology (i.e., tangles) in the frontal cortex. The increase in the number of neurofibrillary tangles in the frontal cortex may be accounting for the slightly different presentation of AD in these patients. It was important to identify these patients so that future studies about potential treatments and caregiving strategies can be done. We are very appreciative to all of the families who have already shared their experiences with us and have and continue to help guide research at the Institute for Brain Aging & Dementia.

You can read the full text of the article titled: “Clinical and Pathological Evidence for a Frontal Variant of Alzheimer’s Disease” in the October 1999 issue of Archives of Neurology at this website: http://archneur.ama-assn.org/issues/current/toc.html
There are many ways to support the UCI Alzheimer’s Disease Research & Treatment Center and the Institute for Brain Aging & Dementia. Below is a list of the many ways you can support both clinical and basic science research activities at the University of California, Irvine. If you would like to receive more information on giving, please contact Elizabeth Eastin at (949)824-8135.

**Outright Gifts**
Outright gifts, such as cash, securities or other property provide the Institute for Brain Aging and Dementia with much needed financial assistance. Outright gifts big or small, have an immediate impact on programs and projects because they can be used to support a variety of current needs.

**Gift Pledges**
A pledge is a formal statement of intention to make a gift. It may be followed by an immediate gift or it may simply confirm your intention to make a gift in the future. Many donors choose to complete their gift pledge by making regular payments over a period of time.

**Gifts with Retained Interest**
Your gift can allow you to hold an interest in that gift for your lifetime or for a specified term of years. After that time, the funds become available to the specified project or program. For example, you can set up a charitable trust that allows you to receive income from that trust for a specified period, or for life.

**Planned Giving**
Planned gifts are gift arrangements that have specific tax advantages and often include lifetime income to a beneficiary or beneficiaries named by the donor. Many UCI Donors have utilized planned giving methods and are enjoying the benefits today: capital gains tax savings, increased income and income-tax savings.

**Gifts of Endowment**
A gift of endowment is a fund that is maintained in perpetuity, and only a portion of the annual investment return is used for the purposes specified by the donor. The rest of the investment yield is returned to principal. Thus, over the years, the fund can grow and hopefully keep up with inflation. Such endowments, which typically bear the name of the donor or donors, reflect your interest and serve as an enduring testament to your generosity.

**Appreciated Securities**
A gift of long-term appreciated marketable securities helps you save taxes twice. Such a gift will provide an income-tax charitable deduction and capital gains tax savings.

**Gifts of Real Estate**
When you give a gift of your home or real property, you may claim an income-tax charitable deduction based on the full market value of the gift, avoid capital gains taxes, and eliminate certain costs associated with the transfer of real property. Gifts of real estate can also provide income to you.

**Unrestricted Gifts**
When you do not restrict the use of your gift, the Institute gains flexibility not otherwise available. The unrestricted gifts can be used to meet the changing or urgent needs at the Institute.
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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Cordula Dick-Muehlke, Ph.D., Clinical Psychologist
Elizabeth Eastin, Clinic Manager
Lori Lewis, Patient Care Coordinator
Shirley Sriyordsa, Administrative Assistant
Catherine Ortiz, R.N., M.S.N., G.N.P., Clinical Trials Coordinator
Hyunmie Kim, R.N., M.S.N., G.N.P., Nurse Practitioner

2000 Family Education Series

February 8    Yes, Alzheimer’s disease is Treatable

June 13   Relationship Issues & Dementia

September 12  Life Enhancing Activities for Persons with Dementia

December 5  Handling Stress During the Holidays and Year Round

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.
**UCI Institute for Brain Aging & Dementia**

**CALENDAR 2000**

Feb. 8 Workshop: Yes, AD is Treatable!

June 2 Annual Research Conference

June 13 Workshop: Relationship Issues

Sept. 12 Workshop: Life Enhancing Activities

October 7 Memory Walk at Irvine Spectrum

Dec. 5 Workshop: Handling Stress

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"Snowed In", by Dawn

Artwork borrowed from 2000 Orange County Alzheimer’s Association “Memories in the Making” Calendar. The Calendar may be purchased by calling (714) 283-1111.

Friday, June 2, 2000

A Day-long Conference

A History of Mice, Men & Women in the Year 2000: Alzheimer’s Disease

**Save the Date:**

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UCI Institute for Brain Aging & Dementia

University of California, Irvine