We often write about the cognitive deficits associated with Alzheimer’s disease. It is important, however, that we also focus on the human face of Alzheimer’s – on the behaviors that often remain intact or are less affected by the disease. In my work as a psychometrist, I often notice that people use humor as a way to connect and convey their understanding of social cues even though they struggle significantly with many of the tests I administer to assess cognitive (thinking) function.

The other day a research participant came in for his annual neuropsychological testing. As I described to him what we would be doing, I warned him that I would be asking a lot of questions. He quickly interjected, “I promise I won’t blush.” On another occasion, I asked a participant, “What state are we in?” He replied, “The state of confusion!” We both laughed as I began the testing.

(Continued on Page 2)
Despite their Alzheimer’s, both of these men were able to maintain a level of witty banter throughout the testing. It’s moments like these that amaze me. Individuals with severe Alzheimer’s, who are unable to perform on most cognitive tests and who struggle invariably in their daily lives, seem to possess an acute ability to make jokes, deliver witty remarks, or chuckle at things most people would find humorous.

**So what’s so funny about humor anyway?** There are many theories about the purpose of humor and our ability to use it in different ways. Charles Darwin and other evolutionary biologists tried to understand why we laugh and what survival value it has, if any. Darwin, among other scientists, believed that laughter may be a tool that humans have developed to cope with stress. Some psychological theories of humor support the idea that humor is adaptive. The “release” theory suggests that humor can help to prevent a person from being overcome by negative emotions that would otherwise cause great pain and/or stress.

**Humor’s Healing Touch.** What do we know about the aging brain and humor? Canadian researchers at the Baycrest Centre for Geriatric Care, University of Toronto conducted a study of humor in older adults to better understand if humor changes with age. Researchers of this study administered a series of neuropsychological tests to assess the participants’ level of cognitive (thinking) ability. They also administered different questionnaires which asked participants to determine correct punch lines for jokes and choose what they considered humorous or not from a number of scenarios. The findings suggest that cognitive (thinking) abilities may deteriorate with aging; however, emotional processing, (including the ability to respond appropriately to humor even without complete understanding of the content) may remain intact. This capacity is important because it means that the person can interact in a social situation. Moreover, humor can enhance quality of life by helping a person cope with stress and the negative effects of getting older. Humor may serve as a means for older adults with diminished levels of cognitive functioning to continue expressing themselves and their personalities.

There is also plenty of evidence that supports the health benefits of humor. Humor often prompts laughter, which has been shown to enhance health through better respiration. Moreover, some research suggests that laughter increases immunity better than simply relaxing. Humor has also been used successfully as a therapeutic intervention for people with dementia and Alzheimer’s disease. Using humor in therapy to elicit a positive response from a patient can help put the person at ease and can help to create a positive rapport between the patient and the clinician. Likewise many caregivers will attest to the experience that a sense of humor elicits positive reactions from those that rely on them and that laughter helps to relieve stress. Psychologists Newman & Stone have suggested that someone who has a sense of humor is better able to “counteract stress or at least better able to moderate its harmful effects.”

Although, we do not yet understand what specific types of humor are understood by persons with Alzheimer’s, we do have evidence that even when thinking abilities begin to suffer, the ability to experience and communicate emotion may remain less affected. Therefore, it is worth recognizing and appreciating that humor can be used by both a person with Alzheimer’s disease and caregivers as an important communication tool. Finally, older adults and some people with Alzheimer’s are capable of providing meaningful, consistent responses that illustrate individual expressions of self. Many people afflicted with Alzheimer’s are trying to hold onto a lifetime’s worth of experience whether they are aware of it or not. Humor may be one of the ways people suffering from this disease can express a part of who they were and perhaps, still are.
Since the early 1990s, staff at the Shiley-Marcos Alzheimer’s Disease Research Center have been providing support groups for persons in the mild-to-moderate stages of Alzheimer’s disease (AD). With advances in earlier detection, many people are being diagnosed when symptoms are mild, yet concerns about the experience and progression of these symptoms can be significant. Common concerns include emotional responses to the diagnosis, how or when to tell others, developing coping strategies for cognitive and functional loss, finding meaningful activity, and struggling with loss of independence. Although many support group facilitators around the world have noted the therapeutic effects of support groups for people with mild-to-moderate AD, it has been challenging to “measure” this effectiveness through formal research studies.

In an attempt to obtain direct feedback from support group participants, we developed a survey to investigate why participants with AD attend a support group, what they like best about their group, their preferences for discussion topics, and any perceived outcomes of participation. A total of 70 people with AD from eight well-established support groups across the United States participated in the survey. We used both rating scales and open-ended questions to obtain responses and can summarize the following findings:

A large majority of people with AD attended their support group primarily for the socialization with others who share their symptoms and for the educational benefits. One respondent replied, “To be with a group that feels the same as I do and has the same problems - I don’t feel strange about revealing what is going on with me.”

Participants most valued discussion topics related to strategies for coping with AD and learning about research and treatment updates. Well over 80% of participants reported that they had more understanding of AD as a result of support group participation and were also better able to cope with changes related to AD. A majority of participants also reported that they were better able to accept their diagnosis, felt less isolated and alone, and less frightened or anxious.

A series of statistical analyses of the responses revealed other interesting findings. More recently diagnosed participants were particularly interested in learning how to cope with AD and in research and treatment updates. They came to a support group seeking information and were eager to learn ways to manage their symptoms. As the disease progresses, it is possible that group participants become more familiar with their condition and may rate learning about it as a lower priority. Statistical correlations also suggested that the longer participants had been in the group, the less interested they were in discussing concerns about social and family relations. Support group participation may ease initial feelings of isolation (as was noted earlier) and make this topic less urgent.

Although many participants reported on the positive effects of their group experience, our survey is biased by those who stayed in their group versus those who tried attending, but did not continue. It is also important to note that almost a third of survey respondents reported that a spouse, family member, or physician recommendation was instrumental in getting them to give a support group a try.

We now understand the processes that lead to the production and removal of Beta-amyloid protein (Aß), the substance that forms sticky plaque deposits in the brain. Many scientists believe that lowering Aß levels in the brain is an important goal of treatment. Another important approach is to target pathways involving tau, a protein that forms the other hallmark brain pathology of AD, the tangle. Basic research advances have resulted in methods to screen for new drugs that affect Aß or tau and animal models for further testing of candidate drugs.

Dr. Michael Grundman, from Elan Pharmaceuticals, Inc., reviewed approaches to reduce the build-up of Aß in the brain by using antibodies. Initial studies showed that after mice that had been genetically engineered to deposit Aß in their brains were immunized with Aß, they raised a strong immune response and made antibodies against Aß that markedly reduced the build-up of brain amyloid and plaques. In 2002, Elan attempted an immunization study in humans using the Aß peptide. This trial was stopped after about 6% of patients on active treatment developed brain inflammation. Long-term follow-up studies on many of the study participants have been encouraging. Of those participants who were contacted, responders showed better performance on cognitive test scores and activities of daily living compared to placebo-treated patients. A series of studies is now underway in which patients are infused with anti-Aß antibodies (‘passive immunization’). To date, these infusions have been safe in patients with mild AD, and Elan recently announced that a larger scale study is being planned. Many other investigators are also studying approaches to active immunization, some of which may be safer than the methods in Elan’s 2002 clinical trial.

Dr. Eric Siemers, from Eli Lilly, Inc., described research focused on gamma-secretase, an enzyme which cuts the parent protein of Aß and many other proteins in the body. This enzyme may contribute to the abnormal cleaving and depositing of Aß in persons with AD. Eli Lilly is working on a “gamma-secretase inhibitor” (LY450139) that has shown promise in lowering Aß production and decreasing plaque build-up in animal models. In a recently completed multicenter study in patients with mild-to-moderate AD, this drug appeared to be reasonably safe. It lowered the levels of Aß in the blood for several hours after each dose. Some side effects were noted, but were not major, and a more comprehensive trial is being planned.
Blocking plaque formation by using drugs that bind to Aβ protein is another approach, discussed by Dr. Paul Aisen, of Georgetown University. A compound called Alzhemed was effective in decreasing amyloid plaques in a transgenic mouse model, and was safe when given to humans. A large-scale study involving over 1,000 patients compared treatment with two different doses of Alzhemed with placebo, and was completed earlier this year. The results of the study are still being analyzed and are expected by the Fall of 2007. Other plaque inhibitors are being developed, including Scyllo-cyclohexanexol, which decreases Aβ deposits and improves cognition in transgenic mice.

Dr. Mark Tuszyński described a series of studies using nerve growth factor, or “gene therapy.” A small initial clinical trial in patients with AD was carried out at UCSD. Patients’ skin cells were initially harvested, and used to grow cells called fibroblasts in the laboratory. These were injected with the gene that makes nerve growth factor. The fibroblasts were then injected into the brains of patients with AD by a neurosurgeon. Initial data suggested that there may have been a slight improvement of symptoms in some of the study participants. This approach has been extended, using a type of virus with the nerve growth factor gene attached, to deliver the NGF gene to brain cells. Although this approach again requires injection into the brain, it is technically easier and may lead to longer lasting gene expression in the brain. This approach is currently being tested in a small number of patients with AD at Rush Medical Center in Chicago.

Dr. Pierre Tariot reviewed approaches to decrease the formation of tangles from the aggregates of the tau protein. Although much is known about tau, it is still not clear exactly how tangles form. Adding phosphate groups to tau is an important regulatory pathway that may influence tangle formation. There are several currently available drugs that can alter tau phosphorylation. One of these, valproic acid, is being studied in a clinical trial in AD. Another, with a stronger effect on these pathways, is Lithium, which has been used for many years to treat bipolar disorder. Treatment with lithium has been shown to decrease tau deposits in an animal model, and a clinical trial in humans with AD is planned.

Dr. Evan Snyder, from the Burnham Institute, reviewed many of the questions surrounding stem cells and AD. He discussed potential applications of stem cells in general. Apart from treatment, stem cells could provide extremely useful tools to develop models of how enzymes and processes relevant to AD could work. Although stem cells are far away from being applied to treat AD, Dr. Snyder presented an analogy: a transgenic mouse strain that has been genetically engineered to be deficient in an enzyme in the brain that leads to changes resembling those of Tay-Sachs disease. In these mice, injecting neural stem cells into the brain led to delay of disease onset and decreased pathology, together with improved movement abilities and prolonged survival in this otherwise lethal disease. Transplanted cells did not simply replace damaged nerve cells, but enhanced communication with many other types of cells within the brain. This is an important concept that may eventually have a bearing on stem cells being used in neurodegenerative diseases such as AD.
A clinical trial is a test or study of a new drug, device, or procedure. The following clinical trials are testing how effectively a medication works in relieving symptoms, diagnosing, or providing treatment for Alzheimer's disease.

Although participation in a clinical trial does require some time commitment with visits to our Shiley-Marcos Alzheimer's Research Center, in many cases, the visits are infrequent. Some people do not want to participate in a clinical trial if there is a chance of receiving a placebo (a look-alike pill with no medicinal ingredients). It is well documented, however, that people who are unknowingly taking a placebo sometimes experience improvement of their symptoms or condition simply because they believe they are taking something that could be of benefit to them. Also, the ongoing support of the clinical trial coordinator can be a rewarding experience that increases feelings of well being for the participants.

Please contact us with any questions or concerns about our clinical trials. We greatly value your participation so that we can continue to make advances in the treatment and cure of Alzheimer's disease.

**Participating in Clinical Trials**

**AAB-001 Elan Pharmaceuticals**

**STUDY DIRECTOR**

Jody Corey-Bloom, M.D., Ph.D.

**TIME INVOLVED**

Approximately 11 visits over the course of 20 weeks

**DESCRIPTION**

This study will assess whether AAB-001 is safe and well-tolerated for use in persons with AD. The investigational drug AAB-001 is an antibody (a type of protein usually produced by white blood cells to destroy other substances in the body). In AD, protein called amyloid gathers in the brain and is thought to cause symptoms like memory loss and confusion. It is hoped that AAB-001 will attach to the amyloid protein in the brain of persons with AD and help the body remove it. This is a randomized, placebo-controlled study with a 75% chance of receiving active study drug.

**REQUIREMENTS**

- Age 50-87
- Diagnosis of mild-to-moderate AD
- Have a reliable study partner
- In stable health
- Able to have an MRI

**COMPENSATION**

Participants will receive up to $200 per year of the study for undergoing the lumbar punctures.

**CONTACT**

Karen Wetzel, M.P.A.S., PA-C, at (858) 622-5800 and ask for the "Passive Immunization Study" kweitzel@ucsd.edu

**Biomarkers in Aging, MCI, and Alzheimer’s Disease**

**STUDY DIRECTOR**

Douglas Galasko, M.D.

**TIME INVOLVED**

Two visits per year for 5 years

**DESCRIPTION**

This study will measure levels of a number of different proteins in cerebrospinal fluid (CSF) and in blood in order to compare these biomarker levels amongst people who have normal cognitive ability, mild memory problems, or early Alzheimer’s disease (AD). Participation involves a lumbar puncture and bloodwork.

**REQUIREMENTS**

- 40-to-90 years of age with no memory problems
- 60-to-90 years of age with Mild Cognitive Impairment (MCI)
- 60-to-90 years of age with Early AD
- In general good health
- No major lower back problems
- Have a reliable study partner

**COMPENSATION**

Participants will receive up to $200 per year of the study for undergoing the lumbar punctures.

**CONTACT**

Helen Vanderswag, R.N.C., B.S.N. at (858) 622-5800 and ask for the "Biomarkers Study" hvanderswag@ucsd.edu

**WHAT IS THE HOME-BASED ASSESSMENT STUDY?**

Currently, in order to participate in a research study, volunteers must visit a clinic to meet with a healthcare professional who collects important information for the study. Such visits are time-consuming for both the volunteers and the staff and they may prevent older, less mobile people from participating. Home assessments using methods such as the telephone, an electronic kiosk or mail-in forms may be a better way to record study information and assess participant changes.

The Home Based Assessment study will evaluate these three in-home types of information gathering and determine how practical each method is. Second, it will find out if these three methods of gathering information can detect a change and a rate of change in both the volunteers' daily living activities and their functional capabilities over time. The final analysis will compare these methods to the traditional way of collecting information in a clinic setting.

**HOW THE STUDY WILL WORK:**

- The study will recruit 600 volunteer participants nationwide.
- Each participant will have an in-person screening assessment visit in the clinic, or at home or at another location. This will include a physical exam, a medical history, a mini mental state exam, and a neurological exam. A small sample of blood will be taken.
- All eligible participants will be randomly assigned to one of three information gathering methods: Mail/Phone, telephone Interactive Voice Response (IVR), or Electronic Kiosk.

**YOU MAY QUALIFY TO PARTICIPATE IF YOU:**

- Have normal mental function
- Are fluent in English
- Are willing to take multi-vitamins provided by the study
- Are able to answer and dial a telephone, have access to secure mail, possess minimal computer skills or a willingness to learn

*A study partner is desirable but not required.*
People become clinical trial volunteers for a variety of reasons. For Evelyn Kleber of San Diego, her participation in Alzheimer’s disease (AD) clinical trials could not be more personal.

She remembers growing up hearing people talk about older adults “going childish.” Then her mother developed Alzheimer’s which later took her life. Evelyn’s sister is now in the late stages of AD and Evelyn knows what she could face. She’s determined to treat her future with knowledge, not rumor and gossip. Evelyn joined her first study at the UCSD Shiley-Marcos Alzheimer’s Disease Research Center in 1998.

“I had heard about the APOE4 study and Dr. Bundy,” Evelyn recalls. “I thought it sounded interesting. I happened to have the time to volunteer as a study subject and I’m always interested in learning more, so it seemed like a good thing to do.”

Since the first study, she has participated in numerous clinical trials and plans to keep volunteering because she admittedly thrives on learning everything she can about the disease and its progression. Evelyn says that by being involved in the studies she gets the most current and reliable information from the researchers and clinicians and that gives her a great advantage.

“I listen to the research people,” she says, adding that this permits her to ignore idle talk and misconceptions. “Plus, my questions are answered well. I feel like I can get on the phone and call anybody anytime I want and get answers.”

There’s one other reason Evelyn participates in the clinical trials. She believes that one person can make a difference in helping to find a cure for AD and that is why she keeps volunteering. “It’s a team effort,” she says, “we all have to do our part.”

It would be easy for Evelyn to believe she is headed for developing the disease herself but she counters the tendency to think about that possibility by staying optimistic.

“I grew up with positive feedback,” she states, “my family is just that way. I don’t know any better.”

Which is why, as long as she is able, Evelyn plans to keep volunteering.
Evelyn Kleber’s Day at the Imaging Center

Evelyn is currently participating in the Alzheimer’s Disease Neuroimaging Initiative. The pictures here are of the day she had her PET and MRI scans done.
The Shiley-Marcos ADRC recently completed a study with Eli Lilly and Company using a novel compound called LY450139. This drug, a gamma secretase inhibitor, targets the process that produces beta amyloid, the component of amyloid plaque that accumulates in the brain in Alzheimer’s disease.

Overall the trial was successful in its goals. It was aimed at proving that the drug is safe and decreases blood or spinal fluid markers of disease. With that goal we found that the drug is indeed safe and effective in lowering blood levels of amyloid, a marker of disease pathology in Alzheimer’s disease. Decreased amyloid levels in the blood may be an indicator that mechanisms producing amyloid plaques in the brain have also been slowed. This trial has provided Eli Lilly and Company with enough information to pursue a larger trial to determine the drug’s benefits in slowing down or stopping the progression of Alzheimer’s disease. Although there were no clinically worrisome side effects related to the drug, it is clear that there is a risk of drug rash and gastro-intestinal symptoms, as well as fatigue and drowsiness. These types of symptoms will need to be monitored in all patients who may receive this drug in the future. The Shiley-Marcos ADRC is excited to continue collaborating with Eli-Lilly in developing this promising treatment.

We know that our health is influenced by both genetic makeup and environmental factors. The results of our study (to be published in Biological Psychiatry in September, 2007) showed that older individuals who have recently experienced highly stressful “real life” events (for example, death of a family member) had more difficulty on tests of memory than those who had not experienced recent, high stress events. Similarly, those who had a specific genetic characteristic known to be a risk factor for Alzheimer’s disease (i.e., the e4 allele of the apolipoprotein E gene or APOE-e4) also showed more problems with memory than APOE-e4 negative subjects.

Perhaps the most interesting result of the study, however, was the interaction we found between genetic status and the experience of high stress events. That is, for some aspects of memory, highly stressful experiences had a detrimental effect only in those individuals who carried the APOE-e4 allele. The results have implications for interventions that could prevent harmful responses to stressful experiences and, as a result, could prevent or slow the progression of cognitive changes in genetically vulnerable, older individuals.

We Are Looking For Children, Grandchildren, and Siblings of People Diagnosed with Alzheimer’s Disease

VOLUNTEER TO PARTICIPATE IN AN IMAGING STUDY TO IDENTIFY EARLY BRAIN EVIDENCE FOR ALZHEIMER’S DISEASE RISK

<table>
<thead>
<tr>
<th>PARTICIPANTS NEEDED:</th>
<th>PARTICIPATION INVOLVES:</th>
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<tr>
<td>✶ Right-handed</td>
<td>✶ Three scheduled visits in one month, including a physical exam, memory testing, and MRI scanning</td>
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<tr>
<td>✶ 25 to 55 years old</td>
<td>✶ There is no cost to participate.</td>
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<tr>
<td>✶ Parent, grandparent, or sibling with dementia</td>
<td>✶ There are no drugs involved.</td>
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<tr>
<td>✶</td>
<td>✶ Financial compensation for your participation.</td>
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FOR MORE INFORMATION, PLEASE CONTACT: Ayesha Sherzai (858) 622-2029

ADRC Welcomes Christina Gigliotti, Ph.D.

I am very happy to have recently joined the ADRC team. Prior to joining the ADRC, I worked in the clinical trials realm as a psychometrist, clinical research coordinator, and recruiter for 18 months while completing my dissertation. I moved to San Diego in 2005 from beautiful Blacksburg, VA, where I earned my Ph.D. from the Department of Human Development at Virginia Tech. My academic focus was Adult Development and Aging; however, my research focused on psychosocial interventions for individuals with dementia, including Tai-Chi, intergenerational programming, Montessori programming, and horticulture therapy. My thesis and dissertation research projects provided me with an opportunity to blend my love of horticulture therapy with my need to contribute to enhancing the quality of life for older adults with dementia.

I grew up in Virginia Beach, VA, which is where my family still resides. I am happy to be in an environment that allows me to blend my homegrown love of the ocean with my many years in the mountains. I first became captivated by the west coast when I lived in Corvallis, Oregon during an exchange program experience at Oregon State. The three moves across the country have enabled me to do quite a bit of traveling and exploring in the nation’s many national parks. My fiancé and I love traveling, camping, and hiking with our dog Arjuna whenever the opportunity presents itself; however, we are also enjoying the many cultural festivals and events that San Diego has to offer.
Memories at the Museum

A collaboration between The San Diego Museum of Art and The UCSD Shiley-Marcos Alzheimer's Disease Research Center
Join us on Friday, October 26th from 2:00-3:00pm at the San Diego Museum of Art, Balboa Park

San Diego Museum of Art docents guide visitors with memory loss through the painting and sculpture exhibits. They facilitate discussions to engage their visual, verbal, and mental abilities, and provide a fun interactive experience. A separate simultaneous tour is provided for an accompanying friend or family member. This program is entirely free of charge to both participants with memory loss and their companions, and is offered quarterly.

Pre-registration is required.
If you would like to participate please contact Lisa Snyder at (858) 622-5800