NEUROIMAGING IS EMERGING AS A SIGNIFICANT, PROSPECTIVE TOOL FOR IDENTIFYING MILD COGNITIVE IMPAIRMENT (MCI) IN CLINICAL TRIALS RESEARCH. CURRENTLY, EXPERTS ARE INVESTIGATING WHETHER NEUROIMAGING STUDIES CAN PROVIDE INSIGHT INTO THE DIAGNOSIS OF MCI, AND IF THESE RESEARCH STUDIES CAN DISTINGUISH PATIENTS WHO ARE MORE LIKELY TO CONVERT TO ALZHEIMER’S DISEASE THAN OTHERS WHO WILL NOT PROGRESS.

NEUROIMAGING USES X-RAYS, MAGNETIC FIELDS, AND/OR RADIOISOTOPES THAT ALLOWs RESEARCHERS TO VIEW A THREE-DIMENSIONAL "SLICE" OF INTACT, LIVING BRAIN. PICTURES CREATED BY DIFFERENCES IN THE SIGNAL INTENSITY OF THE RAYS, FIELDS, AND/OR RADIOISOTOPES ARE COMBINED BY COMPUTER INTO A SINGLE, CROSS-SECTIONAL IMAGE SIMILAR TO A BLACK- AND- WHITE OR COLOR PHOTOGRAPH. NEUROIMAGING TECHNIQUES CURRENTLY USED BY ALZHEIMER’S DISEASE RESEARCHERS INCLUDE CT (COMPUTED TOMOGRAPHY), MRI (MAGNETIC RESONANCE IMAGING), AND SPECT/PET (SINGLE PHOTON/POSITRON EMISSION COMPUTED TOMOGRAPHY).

(Continued on Page 2)
The use of MRI technology to measure brain volume - particularly the size of the hippocampus (a structure deep in the brain that helps code memories for long-term retention) - is done as early as possible in people who may be developing MCI. Researchers at the Mayo Clinic in Rochester, Minnesota, are among the leaders in this emerging field. Under the direction of Clifford Jack, Jr., MD, a team has used this new tool to look at patients with the earliest of memory complaints. Their work has shown that people with MCI have atrophic (smaller) hippocampi when compared to healthy people of similar age. In addition, those with smaller hippocampi and a diagnosis of MCI are more likely to progress to AD than those with larger hippocampi. These imaging results provide biological support for the theory that MCI may in fact represent the earliest known stage of AD. Interpreting neuroimages will likely evolve into a powerful technique in effectively diagnosing MCI.

Unfortunately, hippocampal volumes on the basis of MRI alone will not confirm the diagnosis of MCI or AD, because other pathological processes also can result in hippocampal shrinkage. In the context of a complete neurological evaluation, however, MRI studies can be very useful. Researchers are optimistic that precise hippocampal volumetric measurements will be useful in predicting the rate of progression of the disease. In support of this, Dr. Jack recently reported (Neurology 1999; 52(7):1397-1403) that the rate of change in hippocampal volumes can help distinguish among people with normal memory, people with MCI, and those with AD.

The field of neuroimaging is moving rapidly with constantly evolving technology that will translate into the clinic in the near future. But Ronald Petersen, PhD, MD, Director of the Mayo Clinic Alzheimer’s Disease Center, cautions that brain imaging is unlikely ever to replace autopsy for definitively diagnosing AD. “Imaging studies can give us important information about brain structure and the likelihood of various conditions; but it cannot provide the microscopic information necessary to diagnose AD.” Thus, physical examination of the brain after death will remain necessary to confirm or deny the presence of the disease.” Measuring Brain Volume imaging studies may provide us with important information about brain structure and the likelihood of various conditions; but it cannot provide the microscopic information necessary to diagnose AD.
Images are conjured up of a very sharp, big needle going into your back while being fully alert! Is it even worth going through something like this if it is not medically necessary?

A spinal tap (also known as a lumbar puncture) as part of a research study is by no means a medically necessary procedure. It does, however, enable analysis of certain proteins and hormones in the cerebrospinal fluid (CSF) that cannot be measured through blood tests alone. Thus, while it may not be a medical necessity, it is a medical opportunity to contribute to the growing knowledge of identifying specific proteins or "biomarkers" that may be causing memory disorders such as Mild Cognitive Impairment (MCI) or Alzheimer's Disease (AD).

So, let's talk about what a spinal tap entails. Spinal taps are routine neurological outpatient tests in which a small amount of CSF is removed from the lower part of the back (around the L4-L5 area). The amount of fluid taken is about 1 ounce, which is replaced by your body within 1-2 hours. In our case, the procedure is done here at the ADRC. Once the neurologist locates the area to withdraw the fluid, the area is numbed with a local anesthetic and CSF is withdrawn. Withdrawal takes approximately 5-10 minutes. Once the needle is removed, the person lies down, usually feeling well enough to get up after about 30 minutes. Since only a local anesthetic was given, participants are able to drive home after the procedure.

The most common side effect experienced is headaches. A person may also experience temporary discomfort at the site of the spinal tap. These are usually relieved by taking it easy for a day or two after the procedure, drinking plenty of fluids, resting, and using a mild analgesic. There is a small risk of developing a more severe headache, for which we would provide additional treatment.

Our neurologists have decreased the risk of side effects that may occur from the use of standard spinal needles. Old standard needles "cut" the membrane surrounding the spinal cord, frequently leading to the more severe post spinal tap headaches. We use a very thin, flexible spinal needle in order to avoid "cutting" the membrane. The thinner needles "spread" the membrane apart, allowing the membrane to close up after the needle is removed. Our participants seldom experience a severe post spinal tap headache.

Ideal research candidates for undergoing a spinal tap include individuals without significant back problems (i.e., no previous surgeries), severe deformities; or disease or sepsis in the lower back area. Individuals with bleeding tendencies or on blood thinners are excluded from participation.

We are grateful to those individuals who do undergo spinal taps for research purposes. Your willingness to participate in studies involving undergoing spinal taps is greatly appreciated, and your contribution to science invaluable.
Families with Multiple AD Cases Sought

The National Institute on Aging (NIA) is accelerating the pace of Alzheimer's disease genetics research with a major new initiative to speed the process of creating a large repository of DNA and cell lines from families with multiple AD cases. The NIA's AD Genetics Initiative will intensify sample collection and encourage data sharing by providing access to the repository to qualified investigators.

This new initiative is the result of a series of recommendations made by a team of AD geneticists during a spring 2002 workshop, to speed discovery of risk factor genes that may contribute to late-onset AD. Discovery of these genes is essential for understanding the causes of late-onset AD and for developing appropriate treatments and prevention strategies.

Late-Onset Risk Factor Gene

Late-onset AD is the most common form of the disease, accounting for 90-95 percent of all cases. It usually strikes people 65 years of age and older. Late-onset AD shows no obvious inheritance pattern. However, researchers have identified an increased risk of developing late-onset AD related to the apolipoprotein E (apoE) gene found on chromosome 19. This gene comes in several different forms, or alleles, but three occur most frequently: apoE2 (E2), apoE3 (E3), and apoE4 (E4).

People inherit one apoE allele from each parent. Having one or two copies of the E4 allele increases a person’s risk of getting AD, but it does not mean that AD is certain. Some people with two copies of the E4 allele (the highest risk group) do not develop the disease, and others with no E4s do. The rarer E2 allele appears to be associated with a lower risk of AD. The E3 allele is the most common form found in the general population and may play a neutral role in AD. Scientists cannot determine the exact degree of risk of AD for any given person based on their apoE status.

Early-Onset Risk Factor Gene

Early-onset AD, or familial AD, is much rarer and has been conclusively linked to mutations in three genes - the APP gene on chromosome 21, the PS1 gene on chromosome 14, and PS2 on chromosome 1. If only one mutation on one of these genes is present, early-onset AD will almost certainly occur.

Early-onset AD is the result of an autosomal dominant inheritance pattern, meaning that all offspring in the same generation have a 50/50 chance of developing AD if one of their parents had the genetic mutation. Early-onset AD strikes people as young as age 30.

Late-Onset Gene Search

Scientists have made great progress in the 10 years since apoE4 was identified as a risk factor gene, in narrowing the search for other risk factor genes that may have links to late-onset AD. They have drawn significantly closer to identifying at least four regions of chromosomes where other risk factor genes might be. Intriguing evidence has been uncovered during recent studies, but further analysis of larger sample sets is needed.

Genetic Experts Meet

Recognizing that much larger sets of AD samples is key to continuing the progress made to date and speeding up late-onset AD genetics research, science administrators in the NIA’s Neuroscience and Neuropsychology of Aging Program (NNA) brought together leading experts for a workshop. Their discussions centered on how to expand DNA sample collection, standardize data collection, improve access to that data for funded and commercial researchers, and how to rapidly share data to identify and corroborate new risk factor genes.

Workshop participants agreed that an important component of the NIA’s genetics initiative will be a new emphasis on recruiting large families with two or (Continued on page 5)
Families with Multiple AD Cases Sought

(preferably) more members - known as multiplex families - who have late-onset AD. Collecting blood samples from affected and unaffected family members, to create and maintain cell lines for DNA analysis will aid in the hunt for new genes. This will allow researchers to spend more time on experiments, and less time on the expensive and arduous task of collecting appropriate samples.

"This is extremely important research and we are very pleased to be in a position to recruit subjects to organize sample collection, and to offer well-characterized samples to many of the world's leading AD genetics experts. If the search for risk factor genes is successful, then there are broad implications for future treatments," said Dr. Richard Hodes, NIA Director.

National Cell Repository

A centralized repository at Indiana University - the National Cell Repository for AD (NCRAD) - is expanding its collection facilities as part of this new initiative. Ten Alzheimer's Disease Centers (ADCs) have been provided with supplemental funding to recruit new individuals for genetics research and deposit their blood samples with NCRAD. NIA hopes to gather between 1,000 and 2,000 samples for study.

Families interested in participating may contact Helen Vanderswag, RNC, BSN at 858-622-5800 (hvanderswag@ucsd.edu) or the National Cell Repository for Alzheimer's Disease at 1-800-526-2839 http://medgen.iupui.edu/research/alzheimer/

(Excerpt courtesy of ADEAR, Alzheimer's Disease Education and Referral Center, a service of the National Institute of Aging)
<table>
<thead>
<tr>
<th>Study Title</th>
<th>Study Director</th>
<th>TIME INVOLVED</th>
<th>DESCRIPTION</th>
<th>CONTACT</th>
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<tbody>
<tr>
<td><strong>CLASP Study</strong></td>
<td>Gang Tong, M.D., Ph.D.</td>
<td>8-9 visits</td>
<td>This study involves 8-9 visits over 20 months. Statins are drugs that are used to lower cholesterol to reduce the risk of heart disease. This study will investigate the safety and effectiveness of simvastatin (Zocor) in slowing the progression of AD. Studies in animals have shown a link between lowering cholesterol and decreased severity and risk of AD. Participants will take a study drug for 18 months, and this drug may be provided at no cost. Participation in this study; however, all tests, examinations, and medical care required as part of the study will be provided.</td>
<td>Susan Johnson, G.N.P. at (858) 622-5800 and ask for the &quot;Statin Study&quot;</td>
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<tr>
<td><strong>Huperzine A</strong></td>
<td>Jody Corey-Bloom, M.D., Ph.D.</td>
<td>26 months</td>
<td>This study is to determine whether huperzine A is beneficial in the treatment of mild to moderate Alzheimer’s disease. Huperzine A is a natural cholinesterase inhibitor, derived from the Chinese herb huperzia serrata, used in China to treat AD. Individuals 55 years of age or older who are not currently taking cholinesterase inhibitors and have mild to moderate Alzheimer’s disease are eligible for screening. Treatment with memantine (Namenda) and vitamin E is allowed. Two-thirds of participants will be randomly assigned to receive valproate not only delay the time until such behavioral symptoms as agitation or psychosis emerge, but also slow the expected cognitive and functional decline of AD. This is a randomized, placebo-controlled, double-blind trial of outpatients 55 or older with AD (MMSE 10-20 inclusive) who lack agitation and psychosis and do not require treatment with psychotropic medications. Participants will be randomly assigned to receive valproate or placebo (an inactive substance). Treatment with Aricept (Reminyl), donepezil (Exelon), rivastigmine (Exelon), and/or vitamin E is allowed. Participants will be compensated $200.00 for your participation.</td>
<td>Karen Wetzel, M.P.A.S., PA-C, at (858) 622-5922 and ask for the &quot;Huperzine A Study&quot;</td>
</tr>
<tr>
<td><strong>VALID Study</strong></td>
<td>Jody Corey-Bloom, M.D., Ph.D.</td>
<td>26 months</td>
<td>This is a study to find out whether an experimental drug, ONO-2506, is beneficial in the treatment of patients with mild to moderate AD. This study is sponsored by ONO Pharma, Inc. We are seeking participants who: Are age 50-90 Have mild to moderate AD Are not taking galantamine (Reminyl), tacrine (Cognex), or memantine (Namenda). Treatment with donepezil (Aricept), rivastigmine (Exelon), and/or vitamin E is allowed. Participants will be compensated $200.00 for your participation.</td>
<td>Karen Wetzel, M.P.A.S., PA-C, at (858) 622-5922 and ask for the &quot;VALID Study&quot;</td>
</tr>
<tr>
<td><strong>ONO-2506 Study</strong></td>
<td>Jody Corey-Bloom, M.D., Ph.D.</td>
<td>26 months</td>
<td>This is a study sponsored by Wyeth Pharmaceuticals to find out more about the safety, tolerability and effectiveness of an experimental drug, ONO-2506 in patients with mild to moderate AD. This drug is considered experimental because it has not been approved by the Food and Drug Administration (FDA). We are seeking participants who: Are age 50 and older Have mild to moderate AD Are not taking medications for treatment of their memory</td>
<td>Karen Wetzel, M.P.A.S., PA-C, at (858) 622-5922 and ask for the &quot;ONO-2506 Study&quot;</td>
</tr>
<tr>
<td><strong>SRA-333 Study</strong></td>
<td>Douglas Galasko, M.D.</td>
<td>26 months</td>
<td>This is a study sponsored by Wyeth Pharmaceuticals to find out more about the safety, tolerability and effectiveness of an experimental drug, SRA-333 in patients with mild to moderate AD. This drug is considered experimental because it has not been approved by the Food and Drug Administration (FDA). We are seeking participants who: Are age 50 and older Have mild to moderate AD Are not taking medications for treatment of their memory</td>
<td>Karen Wetzel, M.P.A.S., PA-C, at (858) 622-5922 and ask for the &quot;SRA-333 Study&quot;</td>
</tr>
<tr>
<td><strong>Cerebral Spinal Fluid (CSF) Studies</strong></td>
<td>Helen Vanderswag, RNC, BSN</td>
<td></td>
<td>We are currently looking for participants for a group of CSF studies, some of which involve using CSF (Cerebral Spinal Fluid) to monitor a response to an experimental procedure and others involve looking for novel diagnostic biomarkers for AD. Both normal controls and early to moderate AD participants are needed. These studies will involve lumbar puncture for the withdrawal of cerebrospinal fluid. You will be compensated $200.00 for your participation.</td>
<td>Helen Vanderswag, RNC, BSN at (858) 622-5800 and ask for the &quot;CSF Study&quot;</td>
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Everyone experiences forgetfulness from time to time, from misplacing keys (or worse, your car) to forgetting the name of that neighbor who just moved in. As people age, complaints about memory loss increase and become more worrisome, perhaps because memory loss is the hallmark of Alzheimer’s disease. When people express their concerns to their doctors, they are usually met with questions asking for specifics about the changes, such as "what type of information was forgotten, under what circumstances, when did it start, and how has it progressed?". These questions might seem tedious, after all memory loss is memory loss, right? Well, not quite. Researchers believe that there are at least two different memory systems, and they are affected to a different extent by distinct diseases.

One system directs "declarative" memory, the ability to learn and remember new information and recall or recognize recent experiences. Declarative memory is disrupted by diseases that damage structures such as the hippocampus, vital for encoding new information, directing its storage, and retrieving it when needed. Interestingly, this information is not stored in any one particular area - it is housed throughout the brain in areas called association cortices. When disease damages the association cortices, the information can no longer be retrieved. Alzheimer’s disease has a profound, very early effect on the brain structures that direct declarative memory. This explains why forgetfulness is one of the earliest, most prominent features of the disease. As Alzheimer’s disease progresses, the association cortices that house our memories for past experiences become more and more affected, making it increasingly difficult to recall details about those experiences. **It seems that recent memories are more vulnerable than older ones, which explains why patients often remember details about the house in which they were raised, but not what they ate for breakfast.**

The other system underlies "procedural" memory for well-ingrained habits and skills such as how to walk, talk, and write. Parts of the basal ganglia appear to play a key role. Diseases such as Parkinson’s disease and Huntington’s disease affect these structures and disrupt procedural memory, including the ability to learn new skills. On the other hand, basal ganglia are relatively preserved in Alzheimer’s disease. Research generally finds procedural learning more intact in patients with Alzheimer’s disease compared to patients with Huntington’s disease. In fact, even though patients with Alzheimer’s disease may be unable to learn a new list of words or remember the date, they are able to learn the pattern of a repeating sequence of lights or the movements needed to follow a rotating disk.

**The distinction between declarative and procedural memory explains why an individual who is no longer able to remember the events of the day can still walk into a restaurant, order a meal, and enjoy it.** This distinction is also one of the reasons why your doctor asks so many specific questions about the memory problems that you may be experiencing. Different types of memory loss suggest different diseases.
Alzheimer’s disease (AD) is a progressive degenerative disease of the brain characterized by the presence of plaques, composed of irregularly processed amyloid protein, and tangles, containing abnormally processed tau protein. As a consequence, the patient experiences a decline in the ability to function on a daily basis, impairment of judgment, and problem solving difficulties.

Over time, the majority of patients will experience changes in emotions and temperament which can include anxiety, depression, apathy, agitation, or psychosis. These symptoms become more evident as the disease progresses and contribute to increased caregiver distress and nursing home placement. It is likely that such symptoms are a direct manifestation of impaired brain function.

The mechanisms by which valproate exerts its therapeutic effects in so many neuropsychiatric disorders have not been established. Recent evidence suggests the possibility that valproate affects cellular signaling pathways that are common to all of these conditions. Many of these signaling pathways are important in helping cells resist stressors and contribute to “neuroprotection”. Some of these same pathways are centrally involved in the pathophysiology of Alzheimer’s disease.

These findings suggest that valproate may be a useful treatment for Alzheimer’s disease. Valproate may also regulate a protein (BCL2) that can protect against apoptosis (cell death) and inhibit the enzyme GSK3b, also known as tau protein kinase 1, which may contribute to the development of tangles.

The Valproate Neuroprotection trial ties in all of these themes.

VALID is a randomized, placebo-controlled, double-blind, multicenter, 26-month trial involving 300 outpatients with AD who have not experienced agitation or psychosis yet, but are at risk by virtue of their stage of illness. The study drug, valproate, may have symptomatic efficacy for these types of symptoms once present, and has plausible neuroprotective potential that may be especially relevant for AD. This leads to hope that long-term treatment may not only delay the time until such behavioral symptoms emerge, but also slow the expected cognitive and functional decline.

- Participants will have regular clinic visits as well as telephone contacts for assessment of behavior, cognitive function, safety, and tolerability.
- Blood samples will be obtained and studied to further probe the biological effects of valproate.
- MRI scans will be performed prior to experimental treatment and after one year to evaluate drug-placebo differences in brain measures.
WITH REGARDS TO LAST ISSUE’S REPLY TO A QUESTION ON MEMANTINE:

Q. In the last issue of Currents you answered a question about whether memantine should be used for early to moderate stage AD. The last sentence of your answer stated that “studies in mild AD of memantine combined with Aricept appear to be negative” (...) Can you please clarify your answer in regards to the negative results with the drugs combined?

A. In the ‘Currents’ Dr. Thal stated that ‘studies in mild AD of memantine combined with Aricept appear to be negative’. By negative does he mean it had adverse effects? Or does he mean there were no effects whatsoever?

A. The studies of Aricept and memantine in mild AD were negative in that memantine did not improve cognition beyond that seen with Aricept alone. There were no adverse effects.

Q. I am starting to feel I’m having some memory lapses; often forgetting names of people I know well, and having a hard time coming up with words - sometimes I use the wrong word and am not even aware unless someone corrects me! Could I have AD? What should I do?

A. Dear concerned,

Your complaints may be due to normal aging or to a disease. I would suggest that you seek medical evaluation for this problem.

Alzheimer’s disease research is fascinating and ever-evolving.

If you have questions or concerns about clinical trials, new medications, management of the illness, etc., send them to:

Ask Dr. Thal
c/o Ingrid Padilla
8950 Villa La Jolla Dr. Ste. C-129
La Jolla, CA 92037

or

e-mail us at:
adrc@ucsd.edu

HAVE YOU MET NERV?

(Continued From Page 1)

Nerv, The Aging Neuron, has been named Project Mascot and made its debut at a recent health fair in Casa de las Campanas. MAP introduced him to the general public through its informational display at this fair. He was well received and will continue to make regular appearances in this campaign and all community partnerships associated with this new initiative.

The Memory in Aging Project is headed by Dr. Cecily Jenkins, PhD, who has recently been named Project Director. We have all come to know Dr. Jenkins from all the years she has worked at the ADRC as neuropsychologist for the longitudinal study and other clinical trials, as well as co-facilitating our weekly support group meetings. She will be the main contact person for this project and will be able to answer questions as well as refer study volunteers to individual clinical trials, and perform cognitive assessments.

MAP will start recruiting volunteers by the end of this year/beginning of next. Anyone interested in finding out more about this project may inquire by calling the MAPline at (858) 677-1579.
I Miss Her So Much...

Through his poetry, Jack Goldberg can express some of the grief he is experiencing as Shirley, his wife of 45 years, battles Alzheimer’s disease. His tremendous love for her and sadness over what this disease is doing to her is partly apparent by his 90-mile, every-other-day commute from his home in San Clemente to visit Shirley at the John Douglas French Center for Alzheimer’s Disease in Los Alamitos. “I miss her so much,” Jack said.

Jack and Shirley knew the signs of Alzheimer’s well, because Shirley’s mother, Rose Hertzmark, had Alzheimer’s for more than 10 years. “When I began to see that Shirley was regressing, to recognize what was happening to this beautiful, very smart woman, I knew it was time to try to do something about it,” he said.

So, in addition to writing poetry, Jack, found another way to deal with the tragedy that so many Americans face. He made two generous legacy gifts, first setting up a charitable gift annuity to benefit U.C. San Diego’s Alzheimer’s Disease Research Center (ADRC), and next by including the ADRC in his will. “Supporting research is a way that I, at my age, can help improve the lives of people suffering from this disease who cannot help themselves.”

Jack was impressed by the ADRC and Dr. Thal after reading about them in Healthwise, the newsletter of UCSD’s Stein Institute for Research on Aging (http://sira.ucsd.edu/). He made some inquiries into Dr. Thal’s experience and then met with Dr. Thal and Mary Sundsmo, ADRC Program Director. When asked why he decided to support Dr. Thal’s research, Jack explained, “What impressed me most was that Dr. Thal walked me to my car after our meeting. It showed a courtesy to a stranger in a strange land, and that Dr. Thal is not only a fine doctor, but a fine gentleman.”

At age 90, Jack still lives each day to the fullest. He lifts weights, does calisthenics, and computes math equations without the benefit of a calculator or even pen and paper, to keep his body and mind active and healthy. “I’m very blessed,” he said. “I have the capacity to help. So I do these things.”

For a customized illustration of your potential financial and tax benefits please call Dana Weintraub, Director of Development, at (858) 822-4197 or e-mail her at dweintraub@ucsd.edu.
ANNUAL OPEN HOUSE

Everyone at the UCSD Alzheimer's Disease Research Center would like to cordially invite you to our annual Open House.

Please join us at the La Jolla Radisson Hotel

Wednesday, December 8, 2004
10:00am ~ 11:30am

We will be providing light refreshments and presenting research updates.

RSVP 858-622-5800