Researchers Develop Blood Test to Diagnose Alzheimer's-Type Changes in Mice

by Gila Reckess, Medical Public Affairs, WUSM

Researchers have for the first time used a blood test to identify Alzheimer's-type changes in living mice. The test, developed by researchers at Washington University School of Medicine in St. Louis and Eli Lilly and Company, predicts the amount of amyloid plaque in an animal's brain, a hallmark of Alzheimer's disease. To date, the only way to definitively diagnose this disease in humans is by examining a person's brain after death.

"We don't know if this finding in mice will apply to humans," says David M. Holtzman, M.D., the Charlotte and Paul Hagemann Associate Professor of Neurology and Associate Professor of Molecular Biology and Pharmacology at the School of Medicine. "If it does, it has the potential to provide a non-invasive means of detecting Alzheimer's pathology even before clinical symptoms appear."

Holtzman led the Washington University research team and Steven M. Paul, M.D., group vice president at Lilly Research Laboratories, led the Lilly team. Washington University research fellow Ronald B. DeMattos, Ph.D., was first author; Lilly's Kelly R. Bales, was a co-first author. The study is published in the March 22 issue of Science.

Recent studies have revealed physical changes that can begin in the brains of Alzheimer's patients 10 to 20 years before symptoms arise. For reasons not entirely understood, potentially dangerous amounts of a protein called amyloid-beta (Aβ) begin to build up in these individuals. If enough Aβ clumps together in the brain, it forms amyloid plaques, a key feature of Alzheimer's disease.

"Brain plaques are somewhat analogous to the plaques characteristic of arteriosclerosis," explains Paul. "If you have a heart attack at age 65, the atherosclerotic process that caused that event probably started decades beforehand. Since we now know that Alzheimer's pathology starts well before symptoms appear, we're hoping it may be possible to develop a test that predicts the presence of amyloid plaques and, ultimately, the risk of dementia, similar to performing an angiogram to predict an impending heart attack."

The team examined 49 mice with a mutation in the gene for amyloid precursor protein (APP) similar to the genetic abnormality found in some families with a strong history of Alzheimer's disease. All the mice developed plaques within a year, though to varying degrees. The researchers took advantage of these differences to investigate potential factors that predict the extent of plaque formation.

First, they measured baseline levels of two types of Aβ in the animals' blood, Aβ40 and Aβ42. The mice then were injected with m266 -- an antibody that the team previously discovered draws Aβ out of the brain and into the surrounding blood without harming the animals -- and were periodically retested for blood Aβ. After 24 hours, the researchers examined each animal's brain tissue for plaques, focusing on two key regions involved in Alzheimer's disease: the hippocampus and the cingulate cortex.

Before m266 injection, the amount of Aβ in the animals' blood did not correlate to the number of plaques in their brains. But within five minutes of m266 injection, Aβ levels increased dramatically and did correlate with the amount of brain amyloid. This suggests that blood Aβ levels do not reflect the progression of the disease unless the animal has been given m266.

According to DeMattos, blood Aβ levels in humans also do not reflect the amount of amyloid plaques in the brain. "The truly novel finding of our experiment is that a simple injection of m266 altered the metabolism of Aβ and unmasked important correlations with brain pathology. Hopefully, we also will be able to alter the metabolism of Aβ in humans." The team also developed a rough diagnostic procedure to determine "high" or "low" plaque burden in the animals.

"This has obvious implications for developing a similar blood test for brain amyloid load in humans," says Holtzman. "Though we will not be able to detect risk in someone who has not begun to accumulate amyloid, we hope to predict the disease well before symptoms appear. Such a test also could distinguish individuals suffering from dementia caused by Alzheimer's from those with other types of dementia, and may help us evaluate an individual's response to particular medical therapies."
The 3rd Leonard Berg Symposium, entitled *Neurobiology of the Aging Nervous System: Models, Manipulations & Alzheimer's Disease*, was held at the Chase Park Plaza Hotel on February 15-16, 2002. The Symposium, first organized in 1997, honors founder and former director of the ADRC, Dr. Leonard Berg. This year’s event was sponsored jointly by the ADRC and the Washington University Center for Aging with funding support from Janssen Pharmaceuticals.

Over 200 scientists, clinicians and others were treated to a enlightening series of presentations by a world class faculty. A poster session during the event included 20 studies from Washington University and other institutions, including one submission from KEIO University in Tokyo.

Caleb “Tuck” Finch, Ph.D., from USC, opened the one and a half day symposium with a fascinating talk on the evolutionary theory of aging, which suggests that life-span is determined for each organism by evolutionary forces and therefore may be modifiable. Changes in diet, caloric restriction (CR), and genetic factors, for example, have the potential to extend life, even in humans. “Any lifespan is possible,” says Dr. Finch, under the right circumstances.

**Mark Your Calendars**

**Coming up soon:**

- **Annual MAP-ADRC Participants Meeting**
  
  Topic? Update on ADRC Research
  
  Who? Active research participants & family
  
  When? Saturday, June 8th, 2002, 9 - 11 AM
  
  Where? Junior League, 10435 Clayton Road
  
  RSVP? Call (314) 286-2683

**In the future:**

- **4th Leonard Berg Symposium**

  Topic? Neuroimaging & Alzheimer’s Disease
  
  Who? Health professionals & researchers
  
  When? Fri-Sat, September 19-20, 2003
  
  Where? Chase Park Plaza Hotel
  
  Info? Call 314-286-2882; www.adrc.wustl.edu

**Nun Study Investigator Visits St. Louis**

Pioneering dementia researcher, David Snowdon, PhD, Professor of Neurology, University of Kentucky, visited St. Louis in early February to speak about findings from the Nun Study. For example, he discussed how language skills and education in the pre-teen to teen years may be predictive of dementia in older age. He addressed 100 folks from the WU community on February 6th, and spoke to over 1,200 at an gala event organized by the Alzheimer’s Association the next evening.


An expert in caloric restriction, Richard Weindruch, Ph.D., UW-Madison, presented convincing data that restricted food intake “repeatedly and strongly increases maximum lifespan in rodent models while retarding the appearance of age-associated changes” (quoted from his conference handout). In other words, eating nutritious food but in small quantities allows rats to live longer and healthier lives. Early primates data shows similar results, but human data is still a ways off.

Regarding the aging human brain, Marilyn Albert, Ph.D., from Harvard, showed important data from neuroimaging studies (MRI, PET) suggesting that very early Alzheimer’s disease (AD) can be distinguished from normal brain aging. The hippocampus, a critical memory center, and possibly other brain structures, appear to shrink in early AD and such shrinkage can be detected. In time, physicians may be able to order brain scans to detect very early AD and initiate treatment to prevent significant losses in function. Much more work remains, however, but the initial findings are promising.
Participants in MAP-ADRC Research Support Many Worthwhile Projects: Some ADRC Studies Presented at the American Academy of Neurology, April 2002

Competency to Consent to Research Participation

Presenting Author: Janice Palmer, MSG, Washington Univ.

Ms. Palmer and colleagues explored at what stages in disease progression are persons with dementia still competent to give consent to be part of a medical research study and how this capacity should be assessed. Participants (n=112) were evaluated at the Memory & Aging Project and divided into groups: no dementia, very mild dementia, mild, and moderate. MD's rated them generally as competent, marginally competent, and incompetent. Vignette-based questionnaires about research participation were administered to participants and separate ratings were made based on specific legal standards. A strong negative correlation between dementia severity and competence was found (i.e., the more impaired, the less competent you are). Most persons with very mild dementia (96%) were deemed fully competent under legal standards (78% of those with mild dementia, 43% of the moderates). "Although unstructured MD ratings of competence tended to be more lenient than more formal vignette-based ratings, both methods produced similar patterns, suggesting that MDs are capable of judging the capacity of individuals to give informed consent."

Understanding of Informed Consent by Dementia Research Participants

Presenting Author: Virginia Buckles, PhD, Washington Univ.

How do older adults with dementia who participate in research compare in their understanding of informed consent issues with their unimpaired counterparts? This important question for ethical human studies research was examined by Dr. Buckles and her colleagues at the ADRC. An 11-item questionnaire was administered to 164 participants in the Memory & Aging Project, grouped as having no impairment, very mild dementia, mild and moderate. A score of 9 or more was set statistically as the passing score. All of the unimpaired and very mildly demented participants passed under this criteria, followed by 81% of the mildly demented and 42% of the moderately demented. "These preliminary findings suggest that very mildly demented individuals and most mildly demented individuals understand information conveyed during the consent process." These findings support those of Palmer and colleagues, indicating that mildly dementia persons can retain respond accurately about study participation.

Accuracy of Caregiver Reports in Assessing Individuals with Very Mild to Mild Dementia of the Alzheimer's Type

Presenting Author: Pamela Cacchione, PhD

College of Nursing, University of Iowa

Do caregivers understand how impaired their loved ones with very mild and mild dementia really are? Persons with early dementia (n = 515) were evaluated in the Memory & Aging Project, and their caregivers were asked to rate current impairment on five specific cognitive tasks. Significant relationships were found between caregiver prediction and patient performance on all tasks, indicating general concordance between caregiver reports and actual impairment. The most accurate caregivers lived with the demented person or saw that person more frequently. In general, spouse caregivers were more accurate than adult-child and other dementia caregivers. This study "adds to the growing body of knowledge that supports the use of caregiver reports in the diagnosis of dementia."

ADRC Faculty & Staff Receive Awards

Brian Carpenter, PhD (Psychology) - Received a Brookdale National Fellowship Award to support his research on aging (3/02).

John Csernansky, MD (Psychiatry) - Director of the new Silvio Conte Center for Neuroscience Research following a $2 million research award from NIH (12/01).

James Galvin, MD (Neurology) - Named 3/02 as a Paul Beeson Physician Faculty Scholar in Aging Research. This prestigious award from the American Federation for Aging Research includes a substantial 3-year research grant. Dr. Galvin also recently received a 3-year K08 award from NIA. Finally he was presented the Alene and Meyer Kopolow Award for Geriatric Psychiatry & Neurology from the BJ Hospital Foundation and the WU Center for Aging on April 9th.

David Holtzman, MD (Neurology) - Appointed 8/01 as the first Charlotte and Paul Hagemann Associate Professor of Neurology. This professorship was established by Paul O. Hagemann, M.D., professor emeritus of clinical medicine, and his wife, Charlotte. Hagemann became interested in Alzheimer's research after Charlotte and his brother developed the neurodegenerative disease. Until his death in 1998, he also participated as a control subject in an Alzheimer's study at the medical school.

Marie Meisel, MSN (MAP Satellite Program) - Named "Volunteer of the Year" by the St. Louis Chapter of the Alzheimer's Association (4/25/02)

Consuelo Wilkins, MD (Internal Medicine) - Received a Minority Investigator grant from NIA for her research on AD in African Americans.

Long-time ADRC Secretary Retires

Norma Urani, ADRC secretary for 12+ years, typed her last letter in December, 2001. "It's time to be home with my cats, work in my garden and enjoy my grandkids," she said. Norma, the life of any party, set a festive tone for her retirement luncheon. Hugs and warm goodbyes were the order of the day. Many old WU friends, including Dr. Leonard Berg and his wife Gerri, came to wish Norma well.

After opening gifts, former ADRC Director and founder, Dr. Leonard Berg stood up and praised Norma for her wit, wisdom and dedicated service. Other words of praise followed from current directors, Drs. Johnson and Morris.

"It has been such a joy working with all of you good people," said Norma. "I feel truly blessed to have known and worked with the Best of the Best all these years."

Best wishes, Norma, for a happy, healthy retirement!

Norma with ADRC Co-Directors, Dr. Gene Johnson (left) and Dr. John Morris (right).
## Research Participation Opportunities

<table>
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<tr>
<th>Sponsor</th>
<th>Drug/Item Being Tested</th>
<th>Study Involvement</th>
<th>Volunteer Requirements</th>
<th>Volunteer Benefits</th>
<th>Contact Person</th>
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<tr>
<td>Forest Laboratories</td>
<td>Memantine versus placebo for treatment of mild to moderate Alzheimer's disease</td>
<td>Patient and caregiver will have 7 visits to Memory and Aging over a 26-week period. Patients have a 50% chance of getting Memantine and a 50% chance of getting a placebo.</td>
<td>In good physical health with mild to moderate Alzheimer's disease. Not able to tolerate Aricept, Reminyl, or Exelon. Must have a caregiver who sees them at least one hour per day and can come to all study visits.</td>
<td>No cost medical evaluations and study medication. All patients who complete the 26-week study are eligible to receive active study medicine for at least 6 months after they complete the study.</td>
<td>Angie Berry (314) 286-2407</td>
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<td>Elan Pharmaceuticals</td>
<td>Evaluation of diagnostic tests from Alzheimer's disease - (Elan will use laboratory techniques to test the proteins in blood and urine to try to find a &quot;test&quot; which could diagnose Alzheimer's disease).</td>
<td>Within 2 months after the annual MAP assessment, volunteers will have a one-time morning visit to Memory and Aging to bring in a urine specimen and have blood samples drawn.</td>
<td>Samples will be obtained from controls (people with no memory problems) as well as people with memory problems. Volunteers need to be in good health and on stable medications.</td>
<td>Volunteers will be given a small stipend for their time and effort. Otherwise, there is no benefit. There will not be a test report. Volunteers will not receive money from any medical or scientific products that result from the study.</td>
<td>Mary Coats (314) 286-2303</td>
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<tr>
<td>Alzheimer's Disease Cooperative Study Group</td>
<td>Paper-pencil tests and interviews to detect the earliest signs of Alzheimer's disease</td>
<td>Participants and a study partner will have at least 6 clinic visits over 4 1/2 years. The research paper-pencil tests will be completed by 50% of the subjects/study partners in clinic and 50% will complete the tests at home. A selected group of subjects/study partners may complete the tests via the Internet.</td>
<td>Adults age 75 and over, in good general health with no problems with memory and thinking. Must choose a study partner who has contact twice a week and is willing to accompany the participant to clinic visits and complete the research tests.</td>
<td>Annual evaluations of memory and thinking skills over the course of 4 years. Potential for early identification of memory problems. Compensation for completion of research tests.</td>
<td>Pam Millisap (314) 286-2363</td>
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**Alzheimer's Disease Research Center**

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NHTSA Funds ADRC Driving Study

The National Highway Traffic Safety Administration (NHTSA) is working with the National Institute on Aging and other federal agencies to provide funding for researchers to examine how normal aging and dementia may affect driving. The primary goal of this effort is to help people continue to drive as long as possible, while also ensuring reasonable safety for drivers and passengers alike. As many family caregivers would tell you, balancing a perceived "right" to drive with public safety isn't an easy task where dementia is concerned.

Under the leadership of ADRC Co-Director, Dr. John Morris, a team of ADRC researchers initiated a study in Spring 2002 to examine prevailing attitudes concerning dementia and driving, as well as strategies to encourage person's with dementia who may be unsafe to limit their driving or stop altogether. An important goal of this study is to inform an upcoming NHTSA-sponsored national education campaign. A series of focus group discussions will seek a full range of opinions from persons with early-mild dementia, family caregivers, members of advocacy organizations, health professionals, and traffic/insurance/legal professionals.

"We know that people can remain cognitively and physically healthy into very old age, Aging alone is not a sufficient reason to stop driving," says Dr. Morris. "Even persons with cognitive impairment from dementia, especially those in the very mild stages, can often continue to drive just fine. Some prevailing attitudes are at odds with this viewpoint, however. The challenge is knowing when and how to initiate a driving cessation process. Our study will begin address some of these issues by talking to the people most involved."

Study Underway in Cooperation with Missouri DMV and State Highway Patrol

Dr. John Morris and Dr. Jan Duchek are currently heading up a study to examine the effectiveness of a brief cognitive screening test in detecting unsafe, possibly demented drivers sent to the Missouri Division of Motor Vehicles for license retesting following an on-road incident. The screening test, a short form of the Blessed Dementia Scale, takes about 5 minutes to administer. If found to be predictive of unsafe driving, the "Short Blessed" may be a worthwhile tool for driving evaluators and even by police making road stops to detect a possible driving safety problem. It is important to note that this short test is not foolproof and anyone scoring poorly must receive a full medical evaluation before being labeled as impaired. Screening tests can be very useful, however, in getting an evaluation process started.

Recent ADRC Dementia & Driving Studies

Longitudinal Driving Performance in Early AD
JM Duchek, DB Carr, L Hunt, K Shah, & JC Morris
Manuscript under revision.

This study tested on-road performance of healthy older adults and those with very mild or mild Alzheimer's disease (AD; n=108). The researchers found evidence for decline in driving performance among all three groups, with the greatest impairment evident in the mild AD group. Persons with mild AD were most likely to progress to the "unsafe" category when assessed 6 months after their initial evaluation. Drivers deemed unsafe were encouraged to stop driving and not continue in the study. This study supports a need for regular driving assessment for persons diagnosed with very mild and mild AD.

Characteristics of Motor Vehicle Crashes of Drivers with Dementia of the Alzheimer Type
DB Carr, JM Duchek, & JC Morris

Dr. Carr and colleagues looked at whether there is a difference between crash rates (one indicator of driving safety) and characteristics of older drivers with and without AD (n=121). Main outcome measures in this pilot study were State-recorded traffic crashes and data collected in driving diaries. Persons with mild AD reported significantly less driving exposure (miles per year) than did drivers with very mild dementia or no cognitive impairment at all. Crash rates were low and actually did not differ between groups, although trends suggested that drivers with mild AD may be at-fault in more crashes and be involved in more crashes with injuries. These findings differ from some studies using other outcome measures. A volunteer selection bias may have been involved. Despite this, data from this study does correspond well with findings from a previous ADRC study involving on-road assessment showing that persons with very mild and mild dementia can often still drive safely.
Driving & Dementia: Tips & Tools

Tips for Drivers with Dementia *

- Confide in a friend or family member about what driving means to you. Help them understand what you have to give up when you stop driving.
- Work with your family to create a transportation plan that meets your needs.
- Volunteer to be a passenger. Allow others to do the driving.

Tips for Family Caregivers *

- Observe the person with mild dementia when driving.
- Keep a written record of observable driving behavior over time.
- Share observations of unsafe driving with the person with dementia, other family members and healthcare providers.
- Create opportunities for you or others to drive the person with dementia.
- Ask professionals outside the family to raise questions about driving safety.
- Get information about driving evaluation services in your state or region.

Tips from a Family Caregiver

"Do not tell him he cannot drive per se. The minute I say this, or something to the effect that my mom can no longer drive, she does still get angry and continues to remind me that she is a better driver than many in the road, which may be true. What works with her is if I instill in her head that I (and my brother) am/are responsible for what would/will happen if she drives and something happens. ....."

"Plus, we remind her that she is taking a lot of medication now, and that effects her reflexes.... And, we add on that if someone hit or killed us because they were driving and should not be.... how would she feel, and what would she do? Her car is 1500 miles away, so there is no issue right now. My other problem, is that her doctor actually told her she COULD drive. But I now tell her that her doctor did say she could drive, as long as someone is in the car with her. Which is the truth. So, if someone is in the car with her, that person would be driving...."

Communication from the Alzheimer List (AL), an e-mail based support group for family caregivers and professionals sponsored by the ADRC since 1994. See link at www.adrc.wustl.edu.

Warning Signs Checklist for Drivers with Dementia *

- Have you noticed any of the following warning signs?
- Is there a change in the number or frequency of these warning signs?
- Do the circumstances and seriousness of the warning signs warrant continued close monitoring, driving modifications or an immediate end to driving?

Warning Signs

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- Trouble navigating turns
- Moving into a wrong lane
- Confusion at exits
- Parking inappropriately
- Hitting curbs
- Driving at inappropriate speeds
- Delayed responses to unexpected situations
- Not anticipating potential dangerous situations
- Increased agitation or irritation when driving
- Scrapses or dents on the car, garage, or mailbox
- Getting lost in familiar places
- Near misses
- Ticketed moving violations or warnings
- Car accident
- Confusing brake and gas pedals
- Stopping in traffic for no apparent reason
- Other signs: ____________________________

* Reprinted with permission from At the Crossroads: Alzheimer's Disease, Dementia & Driving, an informational booklet produced by The Hartford Corporation and the MIT Age Lab. This excellent resource can be downloaded from http://www.thehartford.com/alzheimers. A Spanish version will be available in June 2002. To request a paper copy, send a postcard with your return address to "Dementia & Driving Booklet", The Hartford, 200 Executive Building, Southington, CT, 06489.