

Prestigious Honors Flow in 20th Anniversary Year of ADRC

In April, the American Academy of Neurology awarded the 2005 Potamkin Prize for Research in Pick's, Alzheimer's and Related Diseases to John C. Morris, M.D., the Friedman Distinguished Professor of Neurology and director of the Alzheimer's Disease Research Center (ADRC).

This annual prize honors scientists for outstanding contributions to the understanding and treatment of Alzheimer's disease and related disorders. It is regarded as the most prestigious prize in Alzheimer's research. Ronald Petersen, M.D., Ph.D., of the Alzheimer's Disease Research Center at the Mayo Clinic College of Medicine also was awarded the prize this year.

Morris and Petersen were recognized for their pioneering efforts in early diagnosis of Alzheimer's disease (AD).

Among other accomplishments, Morris' research team refined the Clinical Dementia Rating (CDR) system, which was first developed by the founding director of the ADRC, Leonard Berg, M.D., Professor Emeritus of Neurology. The CDR is the standard clinical measure for staging of dementia. Morris' studies have helped clinicians better distinguish between the normal effects of aging on memory and the earliest clinical symptoms of AD.

The impetus to find ways to diagnose Alzheimer's disease earlier stems from a growing awareness of the extent of Alzheimer's brain damage prior to clinical symptoms. Morris, Joseph L. Price, Ph.D., Professor of Anatomy and Neurobiology, and others at the ADRC contributed significantly to this awareness through a series of studies that revealed widespread brain damage in patients only recently diagnosed with AD.

"Our studies illustrate why I accept individual prizes on behalf of the entire ADRC, because they truly represent the group effort of many wonderful colleagues," says Morris.

Morris is the third researcher affiliated with the Washington University ADRC to receive the Potamkin prize. Previous Washington University recipients are Alison M. Goate, D. Phil., the Samuel and Mae S. Ludwig Professor of Genetics in Psychiatry, Professor of Genetics and of Neurology; and David M. Holtzman, M.D., the Andrew B. and Gretchen P. Jones Professor and Charlotte and Paul Hagemann Professor and head of the Department of Neurology.

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According to Morris, this record reflects the extraordinary nature of the ADRC, which celebrates its 20th anniversary.

"First, it indicates that we have a very talented, productive and innovative group of investigators," he says. "Second, these awards reflect the environment in which we work, in terms of our terrific staff and the dedicated volunteers who participate in our studies."

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 With current studies using new brain-imaging agents and other techniques, Morris and his colleagues soon hope to be able to diagnose AD well before the onset of symptoms.

"In the past 10 years, five drugs have been approved by the FDA for treatment of the symptoms of Alzheimer's," Morris says. "In the next 10 years, I predict that we'll be evaluating interventions that not only help the symptoms but also target the underlying factors that cause illness. These treatments will have their optimal benefit when introduced at the earliest possible stage, perhaps even offering hope of preventing the disorder."



John C. Morris, MD, (left) receives the 2005 MetLife Award from Robert H. Benmosche, Chairman and CEO of MetLife, Inc.

In February, Dr. Morris was one of four scientists to receive the prestigious **MetLife Foundation Award** for Medical Research in Alzheimer's Disease.

Established in 1986, the MetLife Award recognizes scientists who have made significant contributions to the understanding and treatment of AD. At the heart of the program is a belief in the importance of basic research, with an emphasis on providing scientists with an opportunity to liberally pursue ideas.

"Alzheimer's is an issue of national importance. It is also a personal issue for many families, as the disease robs them of the person they once knew," said Robert H. Benmosche, Chairman and CEO of MetLife, Inc. "The impact of Alzheimer's on families, society, and the economy is the reason MetLife is committed to the search for a cure."

Dr. Morris was recognized for his work in developing clinical methods to identify the earliest symptomatic stages of AD, evaluating new drug therapies in the treatment of dementia, and establishing phenotypes for inherited forms of AD and other dementia.

Educating Bosnian Elders about Dementia

Did you know that St. Louis has the largest concentration of immigrants from Bosnia in the United States? The Bosnian community here numbers ~40,000, and includes many multigenerational families. For some older residents, barriers of language and/or culture can hinder medical care, especially for memory problems which are often viewed as a normal part of aging.

Over the past year, the ADRC has partnered with the Alzheimer's Association, International Institute of St. Louis, and Bi-Lingual International Assistant Services, to develop an educational video about memory loss for our Bosnian neighbors.

Friends of the partner organizations were recruited to serve as volunteer actors for the project. Jasmina Kusuran-Hawley, the wife of ADRC computer programmer and video editor, Ron Hawley, helped in many ways. Jasmina's mother, Fatima Kusuan, opened her home to the project, cooking a wonderful meal to share with her extended family (and the film crew) during



Grandmother character, played by volunteer actor Razija Caus (far right), demonstrates healthy aging without memory loss.

two dinner scenes—one demonstrating normal aging and another showing the behavior of someone with dementia.

The video, entitled *Recognizing Symptoms of Memory Loss and Accessing Services* (or in Bosnian *Prepoznavanje simptoma gubljenja pamćenja i pristup uslugama*), tells the story of a multigenerational family as they recognize symptoms of memory loss in a beloved grandmother. The granddaughter notices a problem first, raises the awareness of her mother, and then initiates a medical visit. The grandmother is seen being examined by a doctor, and eventually learns that she may have early Alzheimer's disease. A family conference focuses on next steps, and various services are featured.

To obtain a copy of this 22-minute video or to arrange a showing at a local event, please call 314-286-2882 or 314-432-3422 during business hours. We are also currently working with the Alzheimer's Disease Education & Referral Center on a plan for national distribution.



Doctor, played by local Bosnian physician, Dr. Edina Karahodzic, provides feedback to the grandmother and her granddaughter, played by Jasmina Kusuran-Hawley (far right).

Fellows Corner

The training of health professionals is an important activity of the ADRC. In addition to educating students, residents and local health providers, our Center also hosts professionals from other countries. Over the past year, we've had the pleasure of hosting two energetic and committed physicians: Dr. Rajka Liscic from Croatia and Dr. Wee Shiong Lim from Singapore.



Rajka Liscic, MD, PhD

"Being a Fulbright scholar at the ADRC is an exciting and challenging experience. Thanks to my mentor, Dr. John Morris and his colleagues, I'm able to share the latest developments in the field of neurodegenerative

disorders and take an active part in research. For me, a real challenge is to integrate knowledge and experience in daily, ongoing work and to pursue various perspectives that enhance and drive the science forward."

"It has been a wonderful 9 months. Reading the earlier landmark articles of the ADRC, which I came across during the course of my research, further enhanced my understanding of the pioneering work that has been



Wee Shiong Lim, MD

done, and the basis for the unique position that has been taken (e.g. that in the subset of amnesic MCI that "progressed" to AD, the MCI stage represents very mild AD) vis-a-vis other centers. I also enjoy the warmth and hospitality extended by the ADRC family during my 9-month stay."

HORIZONS is the newsletter of the **Alzheimer's Disease Research Center (ADRC)** — a research program in the Department of Neurology, Washington University School of Medicine, funded by grants from the National Institute on Aging and private donations. The ADRC supports and promotes interdisciplinary research on Alzheimer's Disease. The Memory & Aging Project (MAP) — the clinical research office of the ADRC — provides expert clinical assessments of cognitive functioning in normal aging and dementia.

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 **Washington University in St. Louis**
 SCHOOL OF MEDICINE

ADRC Briefs

Adult Children Study

We want to thank everyone who has volunteered for the Adult Children Study (ACS)! We have 85 participants in the ACS who are the offspring of our Memory and Aging Project (MAP) participants. In March, we went to Bethesda, Maryland, for a grant review meeting at the National Institute on Aging. The reviewers asked some tough questions, but ultimately liked many aspects of the ACS application. We've since received the official review forms back and we're hopeful that the study will be funded soon. We are asking our MAP participants (those with memory problems and those without memory problems) to help us recruit their children. An adult child should be 45 to 74 years old, and be willing and able to undergo an MRI scan of the brain and a lumbar puncture. Call Mary Coats for more information (314-286-2303).

Vitamin E

A new study, published in the *Annals of Internal Medicine* (Ann Intern Med 2005; 142: 37-46) evaluated the safety of Vitamin E supplementation using data reported in several previous studies. If you are taking Vitamin E, we suggest that you talk to your physician about whether you should continue taking Vitamin E and the appropriate dosage. This article was distributed in recently in letter form to the private patients of the Memory Diagnostic Center (MDC). Although a definitive statement must await further clinical studies that address the safety and benefits of Vitamin E, the MDC provides the following guidelines:

1. If you are already taking Vitamin E supplements without problems and have no contraindications for taking Vitamin E, the dose should be limited to 400 I.U. or less daily.
2. If you are already taking Vitamin E supplements but after reading the detailed information below prefer not to, you can simply stop the Vitamin E.
3. If you are considering beginning high-dose Vitamin E supplementation, please consult with your primary physician before doing so to ensure there are no contraindications and so that your doctor can fully explain the risks in relation to the potential benefits.

The results of the analysis showed a slightly increased "risk for all causes of death" that was associated with high-dose Vitamin E supplements (i.e., 400 I.U. a day or more). Although the risk was dose-dependent such that the greatest risk was associated with Vitamin E at 1,000 I.U. a day or more, even at the highest doses the overall risk was slight. There was no risk associated for low Vitamin E doses, including the 30- 60 I.U. in multivitamins.

There are several potential problems with the *Annals of Internal Medicine* study, and these problems make it difficult to judge whether the finding of increased mortality with high dose Vitamin E is credible. Because an earlier study published in the *New England Journal of Medicine* (NEJM 1997 336:1216-22) suggested that high dose Vitamin E (2000 IU a day) had modest benefit for Alzheimer patients in slowing disease progression, for years we have recommended Vitamin E in doses of 400 I.U. or greater and have encountered no known problems. However, now we have amended our recommendation for Vitamin E supplements in the treatment of Alzheimer's disease (see above guidelines 1, 2, & 3).

Providing Quality Dementia Care: The Critical Role of the Primary Care Clinician

A CME Conference for Primary Care Clinicians

Presented by:
Washington University ADRC & 5 Other Midwest AD Centers

*Featuring Presentations on Dementia Diagnosis, Treatment,
Neuropathology, Referral Options, & Reimbursement*

When? Friday, June 24, 2005
7:30 AM - 5:00 PM

Where? **Eric P. Newman Education Center**
Washington Univ. School of Medicine

Register? Program and registration information
on-line at <http://alzheimer.wustl.edu>.

5th Leonard Berg Symposium: Antecedent Biomarkers for Early & Preclinical Detection of Alzheimer's Disease

A 2-Day CME Conference for
Clinicians & Researchers

Presented by
Washington University ADRC

When? Friday-Saturday, October 7-8, 2005

Where? **Eric P. Newman Education Center**
Washington Univ. School of Medicine

Register? Program and registration information
on-line at <http://alzheimer.wustl.edu>.

For Pete's Sake

A Play by DaNine K. Ward

Join Us for a Free Dramatic Reading & Discussion

7—9:30 PM, Thursday, November 3, 2005
Touhill Performing Arts Center, UM-St. Louis

Presented by
Washington University ADRC
Alzheimer's Association, St. Louis Chapter
St. Louis Black Repertory Company
Delta Sigma Theta Sorority
Mound City Medical Forum

For Pete's Sake tells the story of Pete, a middle-aged African American gentleman and recent Postal Service retiree with a passion for scrabble, as he faces the reality of memory loss. Join us for this special dramatic reading and walk with Pete, his family, and friends, on a journey of realization, spirited acceptance, and hope.

Visit <http://alzheimer.wustl.edu/adrc2/play> or call 314-432-3422 / 800-980-9080 for more info or to register.

Notables

Michael Avidan, MD, Assistant Professor of Anesthesiology, received a \$29K grant from the Missouri Alzheimer's Disease & Related Disorders Pilot Grants Program (ADRDP) to study cognitive change following major illness or surgery.

Jianxin Bao, PhD, Research Assistant Professor of Otolaryngology, received a \$1.5 million grant from the National Institute on Aging (NIA) to study age-related changes in brain cells.

Ella M. Bolden Brown, friend of the ADRC, nursing educator, and healthcare advocate, was recently awarded one of two 2005 Lifetime Achiever in Health Care awards from the St. Louis American newspaper and Mound City Medical Forum.

Randall Bateman, MD, ADRC Fellow, received a grant from the Barnes-Jewish Hospital Foundation to support an ongoing study of the metabolism of amyloid-beta—the protein which aggregates in Alzheimer's plaques.

Randy Buckner, PhD, ADRC Imaging Core Leader and Howard Hughes Medical Institute Investigator, received two \$1+ million grants from the National Institutes of Health (NIH) to explore cognitive control through functional brain imaging and to develop a Morphometry & Biomedical Informatics Research Network in partnership with Massachusetts General Hospital.

Brian Carpenter, PhD, was recently awarded an *Outstanding Faculty Mentor Award* from the Graduate Student Senate at Washington University.

Alison Goate, DPhil, ADRC Genetics Core Leader and Ludwig Professor of Genetics in Psychiatry, will receive the *Carl and Gerty Cori Faculty Achievement Award* for outstanding research, scholarship, teaching and service, at a special ceremony scheduled for 12/3/05.

Elisabeth Grant, PhD, Data Manager for the ADRC, received the Martin Luther King, Jr., Spirit Award from the University City Board of Education for her work to promote racial harmony.

Yan Hu, PhD, Research Assistant in Neurology, received a \$30K ADRDP grant to study biological markers for Alzheimer's Disease (AD) in cerebrospinal fluid.

Raphael Kopan, PhD, ADRC Investigator and Professor of Molecular Biology & Pharmacology, received \$200K NIH grant to map molecular activity in secretase (enzymes involved in amyloid processing in the brain) interactions.

Petra Nowotny, PhD, Research Instructor in Psychiatry, received a \$29K grant from the ADRDP to study allele specific gene expression as a risk factor for Alzheimer's disease.

Neeraj Pandey, PhD, Fellow in the Galvin Lab, received a \$30K ADRDP grant to study dementia due to the aggregation of the synuclein protein.

Margaret Perkinson, PhD, affiliated investigator of the ADRC, was selected to be Editor-in-Chief of the *Journal of Cross-Cultural Gerontology*. She was also elected a Member-at-Large for service on the Executive Committee of the Association for Gerontology in Higher Education.

Jeffrey Zacks, PhD, Assistant Professor of Psychology, received a 4-year, \$670K grant from NIH to study how the human brain comprehends and processes perceived events.

Celina Zerbinatti, PhD, Research Associate in Pediatric Hematology and Oncology, received a \$30K ADRDP grant to study low-density lipoproteins in amyloid plaques.



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Mouse brain cells rapidly recover after Alzheimer's plaques are cleared

By Michael Purdy

January, 2005 — Brain cells in a mouse model of Alzheimer's disease have surprised scientists with their ability to recuperate after the disorder's characteristic brain plaques are removed.

Researchers at Washington University School of Medicine in St. Louis injected mice with an antibody for a key component of brain plaques, the amyloid beta (Abeta) peptide. In areas of the brain where antibodies cleared plaques, many of the swellings previously observed on nerve cell branches rapidly disappeared.

"These swellings represent structural damage that seemed to be well established and stable, but clearing out the plaques often led to rapid recovery of normal structure over a few days," says senior author David H. Holtzman, M.D., the Charlotte and Paul Hagemann Professor and head of the Department of Neurology. "This provides confirmation of the potential benefits of plaque-clearing treatments and also gets us rethinking our theories on how plaques cause nerve cell damage."

Prior to the experiment, Holtzman and some other scientists had regarded plaque damage to nerve cells as a *fait accompli* — something that the plaques only needed to inflict on nerve cells once. According to Holtzman, the new results suggest that plaques might not just cause damage but also somehow actively maintain it.

The study appeared in the Feb. 5 issue of the *Journal of Clinical Investigation*.

Lead author Robert Brendza, Ph.D., research instructor, began the experiment with one key question: how did clearance of brain plaques, made possible by the development of Abeta anti-

bodies, affect the progression of Alzheimer's disease? Through collaborations with researchers at other institutions, he had acquired several key techniques and technologies that allowed him to closely track changes in live brain cells in mice with an Alzheimer's-like condition.

The mice he used for the study had two mutations. One, utilized by scientists at Eli Lilly, causes amyloid plaques to build up, creating the Alzheimer's-like condition. The second, developed by scientists at Washington University, causes some of the mouse brain cells to produce a dye that allowed Brendza to obtain detailed images of nerve cell branches.

To correlate brain cell changes with plaque development, Brendza injected another dye, developed by scientists at the University of Pittsburgh, that temporarily sticks to amyloid. He showed that as the plaques appeared, nearby branches of nerve cells developed bumps and swellings.

"If you look under the electron microscope at these swellings, they are filled with abnormal amounts of different types of cellular parts known as organelles," Holtzman explains. "Normally any given segment of a nerve cell branch would have only very small amounts of these organelles."

Nerve cells move organelles along their branches as a part of their regular function. Holtzman suspects that this transport breaks down in the mice, leading to pileups that become swellings. Scientists have previously demonstrated that such swellings make it difficult or impossible for nerve-cell branches to send signals.

After showing that the swellings were mostly stable in number and size over

the course of three to seven days, Brendza injected Abeta antibodies directly onto the surface of the mouse brains. In the region of the injection, the antibodies cleared the plaques, confirming earlier research results. Then Brendza closely monitored the swellings for three days.

"We thought that clearing the plaques would halt the progression of the damage—stop the development of new swellings," says Brendza. "But what we saw was much more striking: in just three days, there were 20 to 25 percent reductions in the number or size of the existing swellings."

The nerve cells' rapid ability to regain normal structure has Holtzman and Brendza wondering if the nerve cells are constantly trying to restore their normal structure. If so, that recuperative effort must somehow be countered on an ongoing basis by the effects of the plaques.

More research is needed to determine if similar effects will occur in humans. Abeta antibodies are currently being considered for use in Alzheimer's patients in clinical trials. In the mice, the largest swellings were least likely to heal. Brendza plans to look into whether additional treatment can prompt their recovery.

Holtzman and Brendza plan to continue using the mouse model to study disease treatments and the cellular abnormalities caused by their Alzheimer's-like condition.

"For example, we'd like to know what's going wrong in the nerve cell branches that get these swellings," Holtzman says. "Is it really a cellular transport problem, or do the swellings result from the plaques' effects on nearby support cells? Or is it something else?"

Lumbar Puncture Fact Sheet

Memory & Aging Project (MAP), Washington University

What is a lumbar puncture?

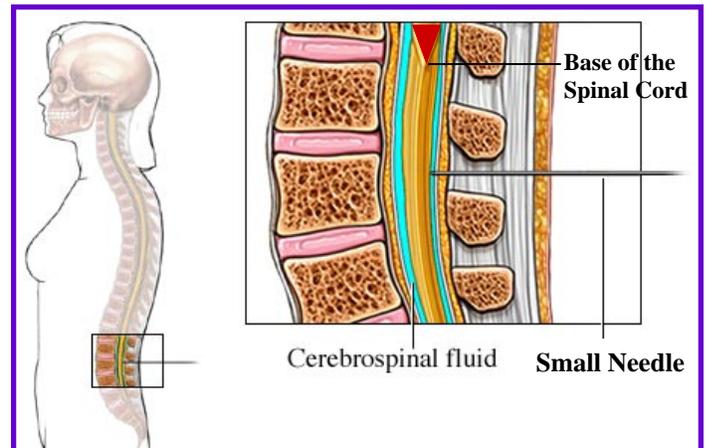
Lumbar puncture (LP), also called a spinal tap, is the procedure doctors use to obtain a sample of cerebrospinal fluid (the fluid that surrounds the brain and spinal cord) for testing. When performed by an experienced doctor, LP is safe and involves minimal discomfort. There is no risk of paralysis.

Research participants who receive an LP through the MAP generally do so while sitting up. The back is scrubbed with a cleansing solution. A local anesthetic medicine is then injected into the skin where the tap will be placed. When the skin is numb, a small needle is inserted into the back at the level of the hip bones, where the spinal cord ends. The needle is pushed forward gently between (not through) the bones of the spine until the spinal fluid is found. For testing, approximately 3 tablespoons of fluid are removed and put into sterile tubes.

Are there risks involved?

You may experience minor pain, bruising or swelling of the skin where the needle is inserted – much as you might when giving blood. A post-LP headache can also occur. Less than 10% of those receiving an LP report a headache. Such headaches are usually mild and last 0-2 days. More severe headaches can occur in rare instances and these usually respond to treatment within a few hours.

A very rare occurrence is infection from the tap itself; the risk for such infection is less than that of a regular blood draw. Persons who faint when giving blood may have a similar flushing/fainting experience in response to LP. All precautions are taken to anticipate potential problems and minimize these risks.



LP involves inserting a small needle between the vertebrae below the base of spinal cord. A small amount of fluid is collected. There is no risk for paralysis.

Why is lumbar puncture important for memory research?

Cerebrospinal fluid (CSF) supplies nutrients to the cells of the brain and spinal cord. CSF contains many of the proteins and other chemicals important for brain health. It may also contain chemical particles indicating a disease process, such as Alzheimer's disease. By testing CSF, researchers hope to identify chemicals that may suggest an increased risk of disease or may be useful in the development of diagnostic tests.

How can I learn more?

Be sure to address any questions you might have with the MAP doctor (314-286-2683). There are also a number of helpful resources about LP available on the Internet:

- **Virtual Hospital, University of Iowa**
<http://www.vh.org/adult/patient/neurology/lumbarpuncturetest>
- **Journal of the American Medical Association**
<http://jama.ama-assn.org/cgi/reprint/288/16/2070.pdf>