# Table of Contents

**Research Highlights**  
1. Strides in Early Detection  
2. Biological and Genetic Risk Factors  
3. Lifestyle Factors  
4. Alzheimer Drug Pipeline  
5. Understanding the Disease Process  

**Alzheimer’s Association Guides Global Research Efforts**  
7. ICAD  
8. International Research Grant Program  
9. WW-ADNI  
10. Research Roundtable  
11. Other Initiatives  

*Alzheimer’s & Dementia: The Journal of the Alzheimer’s Association*  
*ISTAART*  
*Clinical Studies Initiative*

**Funded Research: Changing Lives Today and Tomorrow**  
14. Chad Dickey, Ph.D., 2006 NIRG recipient  
15. Deborah Barnes, Ph.D., M.P.H., 2006 IIRG recipient  
17. Orly Lazarov, Ph.D., 2007 NIRG recipient  
19. Mary Mittelman, D.P.H., 2004 Zenith Grant recipient  
21. Henrik Zetterberg, M.D., Ph.D., 2008 NIRG recipient  
23. Robia Pautler, Ph.D., 2007 IIRG recipient  
25. Giulio Taglialatela, Ph.D., 2008 IIRG recipient  

2008 Alzheimer Science Timeline  
30
Advances in wide-ranging areas of Alzheimer science were made in 2008, from a more complete picture of the cellular and molecular events leading to Alzheimer’s to a better understanding of the influence of genetic and lifestyle factors on disease development and progression.

From among these many diverse lines of investigation, especially strong themes emerged in two related areas: the importance of early detection, including diagnosis of Alzheimer’s disease before the development of symptoms, and the critical role biomarker studies will play in identifying individuals for future clinical trials. Researchers are looking to results from such efforts as the Alzheimer’s Disease Neuroimaging Initiative (ADNI) II to help them identify individuals without symptoms who are at high risk of developing Alzheimer’s and could be enrolled in clinical trials of drugs designed to slow or stop the progression of the disease.

These themes were discussed in an open forum at the Alzheimer’s Association 2008 International Conference on Alzheimer’s Disease (ICAD). Acknowledging these themes, ICAD speaker and Alzheimer’s Association Medical and Scientific Advisory Council Chair Ronald Petersen, M.D., of the Mayo Clinic, remarked, “There is a movement to identify the disease earlier and earlier, and we need presymptomatic biomarkers to do this. A consistent theme has emerged of early detection for early intervention.”

Several exciting discoveries in 2008 reflect these themes.
Strides in Early Detection of Alzheimer’s Disease

Among the discoveries in 2008 that pointed researchers toward paths to early detection of Alzheimer’s disease were those involving the imaging tool positron emission tomography (PET). A high-profile study confirmed that Pittsburgh Compound-B (PIB) binds to the telltale beta-amyloid deposits in the brains of those with Alzheimer’s. PIB, combined with PET imaging, provides researchers with a tool to identify the location and distribution of beta-amyloid deposits. This is a significant step toward enabling clinicians to provide a definitive diagnosis of Alzheimer’s disease in living individuals. A definitive diagnosis is now only possible after death, when brain tissue can be examined for the beta-amyloid plaques and tau tangles that are hallmarks of the disease.

PIB isn’t the only compound researchers used with PET to shed light on Alzheimer’s. PET combined with the radiotracer fluorodeoxyglucose (FDG) enabled researchers in another study to classify different types of dementia with a very high success rate. PET-FDG enables researchers to measure glucose metabolism in the brain. Because glucose metabolism in the brain is decreased in Alzheimer’s disease, FDG-PET may prove a useful tool for diagnosing Alzheimer’s in its earliest stages.

Magnetic resonance imaging (MRI) is well recognized as an instrument for research and diagnosis in many fields of medicine, and research in 2008 showed that it may be useful in Alzheimer’s as well. For example, scientists found that an automated system for measuring the volume of the hippocampus using MRI can help doctors more accurately diagnose Alzheimer’s at an earlier stage. The hippocampus is a region of the brain that plays a key role in memory and learning. In addition, a functional MRI (fMRI) study showed how two regions of the brain prominently affected by Alzheimer’s—the hippocampus and medial parietal lobes—cooperate to form new memories and gave researchers insight into what goes wrong during age-related memory changes.

MRI also helped researchers identify abnormal structural changes in the brains of seemingly normal elderly individuals that aided detection of mild cognitive impairment, a potential precursor to Alzheimer’s disease. In addition, researchers found that MRI scans that detect shrinkage in specific regions of the mid-brain accurately diagnosed neurodegenerative disease such as Alzheimer’s even before symptoms interfere with memory.

Meanwhile, researchers at the Mayo Clinic found that multiple imaging methods, including MRI, magnetic resonance imaging spectroscopy and PET-PIB, each provide valuable information about cognitive function. Using these imaging methods together allowed physicians to better predict an individual’s likelihood of developing Alzheimer’s disease.

Cerebrospinal fluid (CSF) assays are another tool with the potential to reveal biomarkers of Alzheimer’s that could be used for early detection of the disease. For example, researchers showed that the ratio of a protein called beta-amyloid 1–42 to another protein, beta-amyloid 1–40, was reduced in the CSF of individuals who carried the gene for familial Alzheimer’s disease and that levels of two other proteins, t-tau and p-tau181, were elevated before overt symptoms appeared.

Researchers from around the world gathered in July at ICAD 2008 to share advances in areas including early detection and biomarkers. Among the advances discussed were results of a study showing that differences in levels of CD-69, a protein involved in white blood cell growth and production, distinguish between people with Alzheimer’s, people with Parkinson’s-related dementia and those who were cognitively normal. In other biomarker research, a study confirmed previous findings: the more beta-amyloid 1–42 in the brain (as measured by PET scans), the less beta-amyloid 1–42 in CSF.

Additional study results showed that CSF levels of apolipoprotein E (APOE), a protein involved in the
transfer of fatty substances between brain cells, are highly correlated with the levels of proteins known to be involved in the development of Alzheimer’s disease: amyloid precursor protein (APP) and tau. Regulation of APOE levels may affect the levels of APP and tau in the brain.

The scientific community is conducting research to validate these PET, MRI, CSF and other biomarker data. Validated biomarkers will play a key role in identifying individuals in the earliest stages of Alzheimer’s. With this knowledge, individuals are empowered to take action, such as participating in a clinical trial of drugs aimed at slowing or stopping the progression of Alzheimer’s or modifying diet, exercise and other lifestyle factors to improve brain health.

Scientific discoveries in Alzheimer research in 2008 also shed light on a number of other areas of research focus that promise to influence how Alzheimer’s disease is viewed in the years to come.

New Biological and Genetic Risk Factors Uncovered

A vast amount of research in 2008 examined why a person may develop Alzheimer’s disease. Scientists studied factors ranging from levels of vitamins and protein in blood to genetic factors.

Results of one study suggested that low levels of folate, a B vitamin, can triple the risk of developing dementia in older people, while other scientists found that a decrease in the blood protein cystatin C in men ages 70–77 was associated with a 29 percent increased risk of developing Alzheimer’s. Studies examining the ability of blood levels of beta-amyloid 1-42 to predict an individual’s predisposition for developing Alzheimer’s had conflicting conclusions.

Whether dietary supplements have a role in preventing or treating Alzheimer’s has long been queried. Research results published in 2008 included data from one study showing that using vitamins C and E alone or in combination did not improve cognitive function, but another study showed that those with Alzheimer’s who took vitamin E lived 26 percent longer than those who did not. Vitamin B supplementation also did not slow cognitive decline. Additional studies are needed to determine whether dietary supplements have a role in treating Alzheimer’s disease.

A person’s genetics may also play a role in the development of Alzheimer’s. Having two parents with Alzheimer’s is associated with a 42 percent increased likelihood of developing Alzheimer’s by age 70, according to one study. Researchers also found that those who have a mother with Alzheimer’s may be predisposed to the disease. The link may be a malfunction in how the brain metabolizes glucose—something that’s probably genetic and starts years before symptoms of Alzheimer’s appear, researchers said. The researchers found that people with a mother with Alzheimer’s had a much faster reduction in the use of glucose in areas of the brain affected by the disease compared with people who had a father with Alzheimer’s or parents without the disease.

In other genetics research, after studying the genetic profiles of two large Georgia families with high rates of late-onset Alzheimer’s, researchers found a variation in a large family of genes—called TRPC4AP—that may help explain the high rates of Alzheimer’s. The genetic variation is believed to regulate calcium. Calcium is needed throughout the body but abnormal levels can cause inflammation, nerve cell death and possibly plaque formation in the brain.
Some risk factors for heart disease also appear to increase one’s risk of developing Alzheimer’s disease. For example, having health conditions such as diabetes and stroke may impact a person’s risk, reported researchers. In a study involving men only, those who developed diabetes in midlife were one-and-a-half times more likely to develop Alzheimer’s disease than those without diabetes. In another study, individuals who have experienced a stroke and carry the APOE-e4 gene are at greater risk for dementia than individuals with just one—or none—of these factors.

In addition, several studies released in 2008 supported previous reports that those with a diagnosis of depression appear to be at greater risk of developing Alzheimer’s disease than those without a history of depression.

Biological and genetic risk factors for Alzheimer’s such as these provide researchers with a valuable window into the potential causes of the disease and may inform future scientific investigations.

### Lifestyle Factors Influence Risk

Individuals cannot change their genetic make-up, but they can change their lifestyles, and doing so may influence their likelihood of developing dementia. Research results published in 2008 strengthened evidence that exercise, diet, education and an active lifestyle can contribute to maintaining brain health.

Physical fitness may significantly influence one’s risk for developing Alzheimer’s disease. One study suggested that people with larger bellies in their 40s were more likely to have dementia when they reached their 70s. In fact, obesity may increase the risk of Alzheimer’s disease up to 80 percent, said some researchers. Regular, moderate exercise in one’s 50s and 60s may help protect against mild cognitive impairment, and people with early-stage Alzheimer’s who were physically fit as measured by performance on a treadmill test had four times less brain shrinkage than those who did not exercise.

What one consumes may also help ward off Alzheimer’s disease. Flavonoids, compounds found in many fruits and vegetables, may reduce levels of the protein beta-amyloid that goes on to form the amyloid plaques that characterize Alzheimer’s. Investigators also found a benefit in a nutrient-rich drink that might eventually offer a new option in managing Alzheimer’s disease. On the flip side, heavy alcohol consumption (more than two drinks per day) and heavy smoking (one or more packs per day) may hasten the onset of Alzheimer’s by as many as five years.

One study suggested that people with larger bellies in their 40s were more likely to have dementia when they reached their 70s.

The old adage of “use it or lose it” gained ground in several research studies. Scientist discovered that, in babies, the brain generates roughly double the number of nerve cells it needs to function. Cells that receive chemical and electrical stimuli from other cells survive and cells that don’t ultimately die. This could help explain why in one study older persons who had at least a high school education lived 2.5 years longer without cognitive loss than those without a high school education. It also offers insight into how, according to one study of male twins, maintaining social activities and engaging in cognitive activities cut the risk of dementia by 26 percent.
In the ongoing quest for more effective Alzheimer’s disease treatments, 2008 brought both advances and setbacks.

For example, individuals with mild-to-moderate Alzheimer’s disease who received the experimental drug Dimebon experienced improvement in all five outcome measures studied by researchers. What’s more, Dimebon’s benefits seemed to hold, and by some measures even increase, through the trial’s six-month extension study. These persistent benefits distinguish the small-molecule drug from existing approved therapies for mild-to-moderate Alzheimer’s—none of which have shown increasing improvement past 12 months.

Several other drug trials showed promising results. A nasal spray called AL-108 significantly improved some measures of memory in individuals with mild cognitive impairment. The drug targets the fibrous tangles caused by the abnormal build-up of the protein tau. Another drug that aims at breaking up tau tangles in the brains of those with Alzheimer’s is Rember®. Rember showed promise for halting the progression of the disease by improving memory and thinking in people with Alzheimer’s disease.

Phase II results of an anti-beta-amyloid monoclonal antibody—LY2062430—suggested that the drug may begin to dissolve amyloid plaques in the brains of people with Alzheimer’s. Individuals receiving Gammagard, an intravenous therapy derived from human plasma, showed maintenance of cognitive function and, in some cases, improved cognitive function. The drug PBT2 was associated with improved brain function in people with early-stage Alzheimer’s and reduction in the amount of beta-amyloid in CSF.

The vaccine AN-1792, however, cleared beta-amyloid plaques but did not slow the progression of Alzheimer’s disease. The experimental drug bapineuzumab, also designed to remove beta-amyloid plaques in the brain, was linked to a brain-swelling side effect and showed no benefit in the 65 percent of individuals in the study who carried the APOE-e4 gene. But people with Alzheimer’s who did not carry the gene scored an average of five points higher on a 70-point cognitive test. Flurizan®, a drug designed to decrease the production of the protein beta-amyloid, failed to help individuals with Alzheimer’s in its Phase III trial, and Huperzine A, a drug hoped to offer multiple different types of action against Alzheimer’s disease, did not meet its primary study endpoints in its Phase II trial.

Clinical trial results reported in 2008 also included results from studies involving drugs originally developed for conditions other than Alzheimer’s. Results from the largest study of statin drugs, developed for individuals with high cholesterol levels, showed no significant differences in cognition or overall function compared with placebo and Aricept® in people with mild-to-moderate Alzheimer’s. However, a separate study showed that people at high risk for dementia who used statins were half as likely to develop dementia as those who did not take statins.

People who used the painkiller ibuprofen regularly for five years had a 25 percent lower risk of developing Alzheimer’s according to one study. These findings, though, don’t put to rest the debate about the role of non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen in preventing and treating Alzheimer’s. Another study published in 2008 found that NSAIDs do not appear to improve cognitive function in older adults.

These clinical trial results point to the complexity of finding new treatments for Alzheimer’s, as well as the wide array of approaches being used in an attempt to tackle the disease. While several existing medications can improve the symptoms experienced by individuals with Alzheimer’s, none slows or stops the nerve cell death in the brain that is the central cause of Alzheimer’s. Drugs that slow or stop nerve cell death are essential for stemming the epidemic of Alzheimer’s.
Discoveries Advance Understanding of the Disease Process

Clinical trials represent the culmination of years of basic and preclinical research. Without basic research, clinical trials are not possible. In 2008, scientists made numerous basic and preclinical discoveries that helped the field understand how Alzheimer’s develops and progresses.

In 2008, scientists made numerous **basic and preclinical discoveries** that helped the field understand how Alzheimer’s develops and progresses.

For example, an advanced imaging technique showed that beta-amyloid plaques can develop in just one day. In addition, a three-dimensional electron microscopy image of aggregated beta-amyloid was created in 2008 that helped researchers understand the structure and development of beta-amyloid clumps.

In another study, researchers found that blocking a common immune system molecule, transforming growth factor-beta, greatly diminished the formation of beta-amyloid plaques in the brains of mice. It also enabled treated mice to recover some lost memory. Researchers hope the new approach may one day overcome one of the biggest obstacles to the development of new dementia medications—the difficulty in finding drugs that can safely cross the blood-brain barrier.

Another team of researchers learned that elevated levels of the protein ATP-binding cassette transporter (ABCA) 1, which helps move lipids such as cholesterol through the body, sharply reduced the buildup of plaques, potentially slowing the development of Alzheimer’s disease. The study also highlighted a new possibility for Alzheimer treatment: altering the brain’s use of lipids. A separate study showed that naturally occurring lipids found throughout the brain can dissolve plaques. These findings offer new targets for disease intervention.

In other research, lithium was found to inhibit glycogen synthase kinase (GSK) 3β in vivo by disrupting its signaling. GSK-3β is of interest to Alzheimer researchers because inhibiting GSK-3β may decrease formation of the tau tangles that are hallmarks of Alzheimer’s.

Basic science studies such as these provide only a glimpse into the many advances in research made in 2008 toward a better understanding of the development of Alzheimer’s.
In 2008, the Alzheimer’s Association continued to demonstrate its global leadership in nurturing Alzheimer’s disease research.

This position was solidified by record-breaking attendance at ICAD 2008, as well as the funding in 2008 of more than $26 million in research initiatives—the largest in the Association’s 26-year history—to researchers in 15 countries. The Association’s leadership role in advancing the World Wide Alzheimer’s Disease Neuroimaging Initiative (WW-ADNI) also underscores the Association’s global impact, as does the increasing visibility of the Alzheimer’s Association Research Roundtable. The Roundtable is a unique forum for information sharing among members of the pharmaceutical industry in the United States and abroad, academia, the National Institutes of Health and U.S. and European regulatory agencies.

These accomplishments were made possible by the commitment of many. Among them were members from the Alzheimer’s disease scientific community who participate in the Association’s numerous science activities, many on a volunteer basis. These accomplishments also were made possible by leaders of organizations across the continents who share the Association’s vision of a world without Alzheimer’s and with whom the Association has formed essential collaborations. Last but not least, these accomplishments would not have been possible without the individuals from all walks of life who have been touched by Alzheimer’s disease and have taken action through financial support of research to help ensure that Alzheimer’s does not exact its grave toll on future generations.
ICAD

Historically the world’s largest gathering of Alzheimer and dementia researchers, ICAD 2008 broke previous records, drawing more than 5,400 attendees to 2,000-plus plenary, symposium, oral and poster presentations. The conference attracted news media attention both in the United States and abroad, with coverage by outlets including ABC, the BBC, CBS, CNN, NBC, the Associated Press, Reuters, The Wall Street Journal, and USA Today.

Held July 26–31 in Chicago, ICAD 2008 provided a platform for discussion of diverse areas of research, including clinical trial design, genetic factors in Alzheimer’s, biomarkers as tools for early detection and social and behavioral issues in dementia.

Opening the conference, Alzheimer’s Association President and CEO Harry Johns stated that “raising Alzheimer’s from a disease to a cause that is embraced worldwide,” increasing financial support to researchers, and enhancing advocacy efforts to heighten awareness of the epidemic of Alzheimer’s are primary strategic goals of the Association. To accelerate the pace of research and the sharing of research advances, Johns announced that the previously biannual ICAD will be held annually, with ICAD 2009 taking place July 11–16 in Vienna, Austria, and ICAD 2010, July 10–15, in Honolulu, Hawaii.

ICAD 2008 gave attendees insight into the numerous drugs in clinical trials, which incorporated an array of approaches to impact the biological processes associated with Alzheimer’s. “The overarching message is how robust the pipeline is,” said speaker Sam Gandy, M.D., Ph.D., of the Mount Sinai School of Medicine in New York and immediate past chair of the Association’s Medical and Scientific Advisory Council. “Research is moving on all fronts and in unexpected directions.”

The research presented included data from a six-month open-label extension trial of Dimebon showing that the drug produced results similar to those in the preceding 12-month clinical trial. Patients with mild-to-moderate Alzheimer’s who had earlier received the drug for 12 months had preservation of function close to their starting baseline on key signs and symptoms of the disease. Patients originally on placebo who received Dimebon in the extension trial showed stabilization across all key measures studied. Dimebon improves the function of mitochondria, the central energy source of cells.

Also presented were data from a study of intravenous immunoglobulin (IVIg), which resulted in statistically significant improvement in cognitive function in a Phase II trial of individuals with mild-to-moderate Alzheimer’s disease. On the market for more than 25 years as a treatment for autoimmune diseases, IVIg contains antibodies that bind to the beta-amyloid aggregates thought to be central to the development of Alzheimer’s.

ICAD speakers also shared results of a study of methylthioninium chloride (MTC; Rember®) showing that the compound stabilized the progression of Alzheimer’s over 50 weeks in both mild and moderate forms of the disease. MTC inhibits the aggregation of tau, the protein that forms the neurofibrillary tangles associated with Alzheimer’s.

Biomarkers are an area of intense focus by researchers. Studies are underway to prove the accuracy of biomarkers in measuring the physical changes in the brain associated with Alzheimer’s and tracking the progression of the disease. Identifying Alzheimer biomarkers could lead to the development of simple diagnostic tests that would be easily used in physicians’ offices.
International Research Grant Program

In 2008, the Alzheimer’s Association International Research Grant Program funded more than $26 million in research initiatives, the largest annual amount in the Association’s 26-year history of funding Alzheimer research. Providing more funding for Alzheimer research than any other private, nonprofit organization, the Association committed in excess of $250 million to 1,700-plus best-of-field grant proposals between 1982 and 2008. The $26 million includes more than $25.4 million in five grant categories to 131 individual investigators from 15 countries and 26 U.S. states.

The Alzheimer’s Association grant program supports researchers at every stage of their careers. New Investigator Research Grants provide the next generation of scientists with funding that enables them to gather preliminary data, test procedures, and develop hypotheses. Investigator-Initiated Research Grants fund established scientists exploring questions across the research spectrum, from basic neurobiology and genetic risk factors to evidence-based care and disease-modifying treatments designed to slow or stop the progression of Alzheimer’s. Providing $450,000 in research funding over three years, the Zenith Fellows Awards support senior scientists who have made significant contributions to the field and continue to pursue promising lines of investigation about disease mechanisms, diagnosis, novel treatments and quality care.

The Association grant program also funds the Senator Mark Hatfield Award in Clinical Research and the Everyday Technologies for Alzheimer Care (ETAC) Grants. Awarded in partnership with Intel Corp., ETAC grants fund research exploring how computers, monitoring devices and other electronics can be used to meet the day-to-day needs of individuals with Alzheimer’s as well as their caregivers.

In 2008, the Alzheimer’s Association also helped fund the Australian ADNI (A-ADNI), which aims to bring key Australian imaging and biomarker studies in line with ADNI protocols. If successful, A-ADNI will greatly expand the pool of ADNI data and samples available to researchers. Funding also was given to provide an additional year of support to the ADNI Genotyping Project. This research studies the amounts of tau and beta-amyloid in the CSF of individuals who are cognitively normal, individuals with MCI and individuals with Alzheimer’s. Documenting changes in CSF concentrations over time will help establish the potential role of these biomarkers in early detection.

In addition, the Association contributed $100,000 toward the establishment of the Tomorrow’s Leaders in Alzheimer’s Disease Research Award, co-sponsored by the Cure Alzheimer’s Fund and Lou Ruvo Brain Institute. This award recognizes outstanding new M.D. or Ph.D. investigators who have made pivotal contributions to early detection, treatment and prevention of Alzheimer’s disease.
WW-ADNI

The Alzheimer’s Association leads the WW-ADNI effort, which complements the efforts of ADNI. ADNI is a $60 million, 5-year, public-private partnership to test whether imaging technologies (such as MRI and PET), other biomarkers, and clinical and neuropsychological assessment can be combined to measure progression toward Alzheimer’s. ADNI is the first study to examine a number of candidate Alzheimer’s biomarkers in the same individuals. The study is expected to be a landmark for identifying Alzheimer’s biomarkers, with data widely available to researchers. ADNI is primarily funded by National Institute on Aging, part of the National Institutes of Health (NIH), with private sector support through the Foundation for NIH. The Alzheimer’s Association is an ADNI sponsor.

The goal of WW-ADNI is to establish standardized methods across the globe for testing neuroimaging and fluid biomarker tools such as MRI and PET scans and CSF assays. These standardized methods will enable biomarker data obtained at sites worldwide to be pooled, analyzed and used by researchers without concern for the inter-site variability of biomarker data that has played a role in the failure of some clinical trials.

In this role, the Association coordinates WW-ADNI efforts, seeks funding for the continuation and expansion of WW-ADNI and provides support for WW-ADNI partners. It also ensures the steady flow of information among principal investigators conducting WW-ADNI research and facilitates communication between the research community and pharmaceutical companies. By serving as a liaison for the exchange of information between researchers and pharmaceutical companies, the Association plays a critical role in accelerating the pace of clinical trials. When pharmaceutical companies are ready to begin a clinical trial, they can draw upon the information gleaned from Association-led communication activities to identify which researchers have the tools and expertise to lead those trials.

WW-ADNI comprises the North American ADNI (57 sites), European Union ADNI (EU-ADNI, seven operational sites), Japanese ADNI (J-ADNI, 36 active sites) and A-ADNI (two active sites). Specific Association-sponsored WW-ADNI initiatives include financial support for the establishment of EU-ADNI and for activities to ensure integration of A-ADNI data into the North American ADNI database. The Association also fostered discussions to ensure that J-ADNI is carried out in a way that is fully compatible with the North American ADNI and is playing a visible role in cultivating sites for the potential development of ADNI sites in China.

Research Roundtable

The mission of the Research Roundtable is to facilitate the development and implementation of new treatments for Alzheimer’s disease by uniting researchers with diverse affiliations to collectively address issues and obstacles related to Alzheimer research. Begun in 2003 with four sponsors, the Research Roundtable is an undeniable success story. The consortium now includes more than 20 corporate sponsors from the pharmaceutical, biotech, imaging and cognitive testing industries. Each sponsor sends several senior scientists to the Roundtable to benefit from the collegial interactions and networking opportunities available at this unique forum. Additional attendees include scientists from academia; regulatory agencies such as the U.S. Food and Drug Administration and its European equivalent, the European Medicines Agency; and the National Institutes of Health.
The spring 2008 Research Roundtable, held April 29–30, in Washington, D.C., addressed the use of scales as outcomes measures of Alzheimer’s disease clinical trials. Bringing focus to the meeting, William H. Thies, Ph.D., Alzheimer’s Association chief medical and scientific officer, remarked, “Without scales, how do we tell if drugs are doing any good? And how do we know what the outcome measures of scales mean in patients’ everyday lives?” Added Roundtable co-chair Ronald Black, M.D., senior director of clinical research at the pharmaceutical company Wyeth, “Measurement is at the core of clinical trials. If you care about clinical trials, you care about scales.”

Topics at the Roundtable meeting included existing scales and scale development, measures sensitive to change in early Alzheimer’s, computerized measures, and measures useful for early-phase trials. When disease-modifying medications become available, scales will play a key role in identifying patients who might benefit from these medications as well as assessing their effectiveness.

Researchers returned to Washington October 20–21 to share “lessons learned” in designing clinical trials of disease-modifying drugs. Attendees also heard about the role of biomarkers in clinical trials and about trial design strategies employed in studies under way.

Keynote speaker Richard Mohs, Ph.D., of pharmaceutical company Eli Lilly & Company reflected on a Roundtable meeting he led in 2005 that addressed optimal trial design for disease-modifying drugs for Alzheimer’s. “In 2005, looking at fields such as multiple sclerosis and rheumatoid arthritis, the lessons learned were that for each condition, multiple therapies were on the market; biomarkers were used in the diagnostic process, each in different ways; and there were many potential paths for new drugs,” he said. “Since then the science underneath Alzheimer’s has advanced to show potential underlying drivers of Alzheimer’s…. And we have candidate drugs we can test because of this basic science knowledge. Compared with 2005, we now have better tools to measure the pathogenesis of Alzheimer’s.”

These tools include biomarkers such as brain volume and rate of change of brain volume over time; measurements of glucose metabolism and beta-amyloid plaques and other beta-amyloid aggregates in the brain; and levels of beta-amyloid, tau and phosphorylated tau in CSF. With these and other biomarkers, said Dr. Mohs, “It is incumbent upon us to pick the ones that will be most informative in clinical trials.”

The complexity of Alzheimer’s, he added, is that unlike clinical trials that led to the development of disease-modifying statin drugs for heart disease, Alzheimer drugs aimed at disease modification do not have a discrete set of outcomes (such as low-density lipoprotein level in heart disease), but a continuum of outcomes because Alzheimer’s disease progresses on a continuum.

Lessons learned about clinical trial design were shared by scientists involved in the testing of such high-profile drugs as Alzhemed® and Flurizan®, which ultimately were not successful in meeting their desired outcomes, as well as other drugs, including huperzine A, phenserine, LY450139 and bapineuzumab.
Other Initiatives

In 2008, the Alzheimer’s Association’s role in advancing Alzheimer science was also evident by the success of its bimonthly, peer-reviewed journal, *Alzheimer’s & Dementia: The Journal of the Alzheimer’s Association*; new professional society, the Alzheimer’s Association International Society to Advance Alzheimer Research and Treatment; and Clinical Studies Initiative.

**Alzheimer’s Association International Society to Advance Alzheimer Research and Treatment (ISTAART)**

Bringing together researchers and clinicians from a broad range of fields to accelerate progress in Alzheimer’s and other dementia research is the mission of ISTAART, which was launched in January 2008.

ISTAART provides a forum for the sharing of cutting edge research advances from diverse disciplines. The society welcomes members from fields including biochemistry, genetics, geriatrics, molecular and cell biology, neurology, neuroscience, pathology, pharmacology, psychiatry, psychology, radiology and the social sciences.

As the official journal of the Alzheimer’s Association, *Alzheimer’s & Dementia* is circulated to the members of the Association’s International Society to Advance Alzheimer Research and Treatment, as well as other subscribers and libraries. *Alzheimer’s & Dementia* addresses challenges facing researchers, clinicians and health policymakers and features breakthrough research and new thinking across diverse areas of investigation. The interdisciplinary journal provides the impetus for new scientific initiatives and offers probing, thought-provoking studies, articles, and reviews from the leading minds in the field.

By year’s end, ISTAART had nearly 1,000 members.

Steven T. DeKosky, M.D., dean of the University of Virginia School of Medicine and former director of the Alzheimer’s Disease Research Center at the University of Pittsburgh, chairs ISTAART’s Executive Advisory Committee. Says Dr. DeKosky, “Over the past 20 years, Alzheimer researchers and the Alzheimer’s Association have worked together to advance research in the disease, provide information for dissemination to the public and inform Congress and the press about the disease and its implications for social, economic and personal well-being. Now the Alzheimer’s Association has initiated ISTAART, an organization of and for Alzheimer researchers, to foster research in the disease and facilitate interaction among researchers. It is our hope that ISTAART will enable convenient and productive collaborations among members and speed progress in defeating Alzheimer’s.”

As the official journal of the Alzheimer’s Association, *Alzheimer’s & Dementia* is circulated to the members of the Association’s International Society to Advance Alzheimer Research and Treatment, as well as other subscribers and libraries. *Alzheimer’s & Dementia* addresses challenges facing researchers, clinicians and health policymakers and features breakthrough research and new thinking across diverse areas of investigation. The interdisciplinary journal provides the impetus for new scientific initiatives and offers probing, thought-provoking studies, articles, and reviews from the leading minds in the field.

“Alzheimer’s & Dementia: The Journal of the Alzheimer’s Association”

In July 2008, publishing company Elsevier announced that *Alzheimer’s & Dementia: The Journal of the Alzheimer’s Association* (www.alzheimersanddementia.org) had been selected for inclusion in MEDLINE. MEDLINE is the bibliographic database of the National Library of Medicine, containing more than 16 million journal article citations, with a concentration on biomedicine. MEDLINE is a key information source for biomedical researchers.

“The entire editorial board and I are extremely pleased that *Alzheimer’s & Dementia* is being added to the MEDLINE journal collection so soon after its launch in 2005,” *Alzheimer’s & Dementia* Editor Zaven Khachaturian, Ph.D., commented. “Inclusion in this prominent database signals recognition of the journal’s scientific merit and contribution to the field of Alzheimer’s research. More importantly, MEDLINE indexing will help researchers and other interested parties worldwide locate articles published in *Alzheimer’s & Dementia.*”

As the official journal of the Alzheimer’s Association, *Alzheimer’s & Dementia* is circulated to the members of the Association’s International Society to Advance Alzheimer Research and Treatment, as well as other subscribers and libraries. *Alzheimer’s & Dementia* addresses challenges facing researchers, clinicians and health policymakers and features breakthrough research and new thinking across diverse areas of investigation. The interdisciplinary journal provides the impetus for new scientific initiatives and offers probing, thought-provoking studies, articles, and reviews from the leading minds in the field.

By year’s end, ISTAART had nearly 1,000 members.
Clinical Studies Initiative

The pilot program of the Alzheimer’s Association Clinical Studies Initiative was launched in April 2007 to address daunting facts. Among them were statistics indicating that of the more than 9,000 interventional studies under way in the United States, 80 percent were delayed because of enrollment shortfalls. The challenge of recruiting and retaining study participants has become a significant impediment to developing next-generation drugs.

The Clinical Studies Initiative was formed to find effective ways to mobilize and motivate study participants in an effort to accelerate clinical research. Recruitment strategies were tested with the assistance of Association chapters headquartered in five pilot cities: Atlanta, Georgia; Indianapolis, Indiana; Providence, Rhode Island; San Francisco, California; and Tulsa, Oklahoma.

After completion of the pilot program, 38 percent of respondents at pilot sites reported that calls about participation in Alzheimer clinical studies had increased, while respondents at non-pilot sites said it remained the same (71 percent) or decreased (21 percent). In addition, 54 percent of respondents at pilot sites said the number of individuals screened for Alzheimer clinical studies had increased, while 57 percent of respondents at non-pilot sites said it had decreased.

With these successes as a springboard, in 2008 the Association announced the expansion of the Clinical Studies Initiative to 10 chapters headquartered in the following locations: Phoenix, Arizona; San Diego, California; Chicago, Illinois; Timonium, Maryland; Watertown, Massachusetts; Portland, Oregon; Philadelphia, Pennsylvania; Fairfax, Virginia; and Seattle, Washington.
While research conducted today may take years to influence clinical practice and the lives of people living with Alzheimer’s disease, funding for that research has an immediate effect on the scientists whose work is supported.

Receiving Association funding can play a critical role in advancing scientists’ research and, for some, put them on a path toward becoming leaders in Alzheimer and dementia research. In their own words, investigators Drs. Chad Dickey, Deborah Barnes, Orly Lazarov, Mary Mittelman, Henrik Zetterberg, Robia Pautler and Giulio Taglialatela describe their research and what receiving Association funding has meant to their careers.
“Without support from the Alzheimer’s Association, the following work may never have been done. Moreover, it is quite possible that I might have left science or changed fields simply due to the extremely challenging funding environment that currently exists in science as a result of the economic crisis we face in the United States.

With the $100,000 provided by the Alzheimer’s Association, we implemented a novel screening technique that not only identifies drugs that may be new treatments for Alzheimer’s disease, but also sheds light on new mechanisms for identifying better drug targets in the future. In particular, we have focused on using chemicals to promote recycling and clearance of the tau protein, which accumulates in abnormal amounts in the brains of those with Alzheimer’s.

We found that over-expression of mutant human tau impairs the turnover of otherwise normal tau in the mouse brain. We also found that young mice are capable of clearing tau while older animals are not. In addition, we found that heat shock proteins, which are essential for preserving tau in the brain, were present in low levels in young mice relative to old mice. This could indicate that heat shock proteins are contributing to tau pathology.

Using drugs from our screen that inhibit heat shock proteins, we found that if other proteins are accumulating in the brain at the same time as tau, there might be a cellular ‘log-jam’ at the protein clearance system, leading to aggregation of tau.

Other drugs identified from our screen were then tested in mice. Twenty-four hours after injection we found that methylene blue (MB) and its derivative azure C (AC) could effectively lower tau levels in the brain. We are currently analyzing data from a long-term study with MB that show that memory function is improved in mice treated with MB compared with untreated mice. We also saw a reduction in tau levels in mice treated with MB.

We are combining some of these therapies based on their mechanism of action to improve efficacy. Interestingly, MB was recently proposed to inhibit tau protein aggregation, and this function, coupled with its low toxicity profile, propelled it into clinical trials for Alzheimer’s, where it has been met with guarded enthusiasm.

Through our screen and subsequent work, we have identified that MB reduces tau levels by inhibiting a heat shock protein called Hsp70. In collaboration with the Gestwicki Laboratory at the University of Michigan, we have found that Hsp70 activators significantly increased tau levels. Collectively, these data demonstrated that the breakdown of tau is rapidly facilitated when Hsp70 is inhibited by MB. It also suggests that Hsp70 activity prevents the degradation of tau, under-scoring its value as a therapeutic target for Alzheimer’s.

Thus, while the use of MB in the clinic is entering Phase III clinical trials for the treatment of Alzheimer’s disease, its role as an aggregation inhibitor may be superfluous to its more important function of inhibiting Hsp70 activity. By identifying the primary target of MB as Hsp70, the development of more potent Hsp70 inhibitors with superior ability to cross the blood-brain barrier can begin. This discovery could prove to be a critical cornerstone for other
neurodegenerative diseases and make Hsp70 inhibition a viable therapeutic approach. By identifying Hsp70 as a major contributor to tau degradation, we have a more complete understanding of how Alzheimer’s disease starts.

The faith that the Alzheimer’s Association places in junior investigators by providing them with a possible funding source has been critical for progress in the field. By providing an influx of new ideas and scientists in the Alzheimer community, therapies that likely would never have been considered may get to the clinic for Alzheimer’s patients.

One of the things that the general public is likely unaware of is the expense of basic research. This comes in the form of supplies from biotech companies, housing costs for animals and, most important, salary support for the scientists and students involved in the research efforts.

As the recipient of a New Investigator Research Grant (NIRG), I can personally attest that without the grant, I would not have had the same success that I had early on in my training. I received the NIRG one year after I was promoted from a post-doctoral position to an assistant professor at the Mayo Clinic. The NIRG gave me the autonomy I needed to pursue my own ideas, which then led to subsequent funding from the National Institutes of Health. The NIRG funds, coupled with the additional resources I secured as a result, allowed me to take a promotion at the University of South Florida and eventually be retained into a tenure-track position where I received start-up funds from the University and laboratory space in the Byrd Alzheimer’s Institute.

To be quite frank, I likely would have changed to the cancer biology field had it not been for the NIRG I received from the Alzheimer’s Association simply because the funds available for cancer research are so much greater than for Alzheimer’s. Providing these grants to new investigators at a stage when we are just establishing ourselves in the field gives us just enough resources to persevere in our work on Alzheimer’s despite the poor economic climate. These funds provide the foundation for future clinical successes in Alzheimer’s, as evidenced, in small part, by the progress we have made over the past three years toward our ultimate goal: to identify drugs that modify the biological processes leading to the accumulation of tau and perhaps improve the quality of life for millions of people living with Alzheimer’s.’’

— CHAD DICKEY, PH.D.
My research program focuses on identification of factors that may protect against Alzheimer’s disease and other dementias and on evaluation of interventions to enhance cognitive function and delay dementia onset. Several of my prior studies have examined the potential protective effects of mental activity on cognitive function in older adults. In one study, we found that older adults with higher literacy levels had better cognitive function on a wide range of measures. I also was a co-investigator on a pilot randomized controlled trial (RCT) to determine whether a computer-based mental training program could improve cognitive function in older adults with mild cognitive impairment.

In addition, I have conducted several studies of the potential beneficial effects of physical activity on cognitive function in older adults. My colleagues and I performed one of the earliest longitudinal studies in this area in which we found that older women who reported engaging in more physical activity were less likely to experience cognitive decline over 6 to 8 years of follow-up than those who were not as physically active. Because we were concerned about the potential for bias related to self-report of activity levels in this study, we conducted two studies that used more objective physical activity measures, including cardiorespiratory fitness as assessed by peak oxygen consumption during exercise treadmill testing and daytime movement as assessed by an activity sensor worn on the wrist. These produced similar results to those of our earlier studies. Evidence from our work and the work of others led us to publish a review article calling for RCTs to determine whether exercise can prevent dementia in at-risk elders.

Funding from the Alzheimer’s Association combined with a Career Development Award from the National Institutes of Health (NIH) enabled me to launch my first independent RCT. In this trial, we are building on our prior work by comparing the effectiveness of physical and mental activity for enhancing cognitive function in non-demented, inactive older adults who report a recent decline in memory or thinking. This trial, called the Mental Activity and eXercise (MAX) Trial, uses a double-blind, factorial design in which participants are randomly assigned to a mental activity intervention or control group and an exercise intervention or control group. This design will enable us to compare the effectiveness of physical and mental activity and to determine whether they have synergistic effects if combined. This type of research has been identified by the NIH as a high priority research area.

The MAX Trial has been highly successful to date. We have enrolled 123 volunteers over the first 18 months. Sixty percent of volunteers are women, and 40 percent are Hispanic or non-white. Retention has been excellent, with an 80 percent completion rate. In addition, compliance has been outstanding, with subjects attending an average of 87 percent of the exercise classes. MAX trial activities have received high ratings overall from participants (8 to 9 on a scale from 1 to 10, with 10 being the highest). We plan to close enrollment at the end of 2009 and make study results available.
available in 2010. We also are beginning to perform one-year follow-up evaluations in MAX trial participants to determine whether the effects of the interventions are maintained over time.

Interventions such as physical and mental activity have tremendous potential to be effective weapons in the fight against Alzheimer’s and other dementias. Because the incidence of Alzheimer’s increases so dramatically with age, interventions that can delay disease onset by as little as a year or two could prevent millions of people from ever developing symptoms. Funding from the Alzheimer’s Association has been critically important for me to begin to establish myself as a leader in efforts to identify effective interventions for the prevention of Alzheimer’s and other dementias.”

— DEBORAH BARNES, PH.D., M.P.H.
The benefits of physical and mental fitness for prevention of age-related illnesses are unequivocal, and it is reasonable to assume that it would have comparable advantages for prevention of age-related neurodegeneration such as in Alzheimer’s disease. While strategies for physical and mental fitness are common in hopes of preventing Alzheimer’s, the mechanism underlying these strategies is poorly understood. Moreover, how do we ascertain the most effective tactics for preventing Alzheimer’s disease?

Animal models can be very useful for identifying key variables by which one’s environment and experience may affect the development and progression of disease. In our study, we proposed to let mice with the familial Alzheimer’s disease (FAD)-linked mutant gene APPswe/PS1ΔE9 experience a complex environment and examine its effect on the development of Alzheimer’s-like changes in the brain and on critical aspects of brain plasticity (the brain’s ability to change in response to a stimulus, such as learning). These aspects were the development of new neurons in the hippocampus, the seat of memory and learning in the brain, and long-term improvement in the communication between neurons in the brain, called long-term potentiation (LTP).

We showed that experience in a complex environment rescued mice’s ability to generate new neurons in the hippocampus. This was accompanied by significantly reduced levels of hyperphosphorylated tau protein and the oligomeric forms of beta-amyloid, precursors of Alzheimer’s disease, in the hippocampus and cortex of mice. In collaboration with Drs. Gustavo Pigino and Scott Brady at UIC, we observed that experience in a complex environment was linked to enhanced expression of neuronal anterograde motor kinesin-1, a protein that facilitates the transport of nutrients and subunits of the cell from the cell body to the synaptic terminals, the ends of axons where chemical messengers are released from one neuron,
Our research suggests that physical and mental stimulation can rescue critical aspects of brain function that are impaired in Alzheimer’s disease and that methods that encourage brain plasticity may help prevent or treat Alzheimer’s disease. The Alzheimer’s Association was instrumental in its support and contribution to this study.

— ORLY LAZAROV, PH.D.
In 2004, I received a Zenith Fellows Award from the Alzheimer’s Association to systematically test, for the first time, the effectiveness of counseling for couples in which the husband or wife had early-stage Alzheimer’s disease. While couples counseling is an established therapeutic modality and clinicians may offer it in their practices, it had not been rigorously evaluated in this population.

Our hypothesis was that counseling the members of the couple together would significantly improve their relationship. With the support of the Zenith Fellows Award, we developed a couples counseling intervention to focus directly on relationship distress. The intervention was tested through a pilot study at the Center of Excellence on Brain Aging at New York University’s Langone Medical Center. The goal of the intervention was to focus on the couple as a unit. Individualized and emotion-focused, the intervention was designed to support the relationship, mitigate negative effects of the illness and potentially reduce depression for both individuals. The counseling sessions provided a supportive environment in which members of the couple could share their emotional reactions to the diagnosis with each other. Helping couples address their current reactions and consider future plans and needs was one of the key roles of the counselor.

The intervention consisted of six counseling sessions in two months. Forty-one couples were randomly assigned to receive the intervention immediately (20 couples) or participate in the control group (21 couples) and receive the intervention afterward if desired. Comprehensive written assessments were recorded at baseline and at the two- and four-month follow-up sessions. After the four-month follow-up, couples in the control group were offered the intervention. All participants received ad hoc counseling from the time of enrollment. Among well spouses, 61 percent were women. The average age of the well spouses was 72.8 (range, 52–89); the average age of people with Alzheimer’s was 76.3 (range, 55–91). Assessment and intervention were available either at the Alzheimer’s Disease Center at New York University or at home; four of the 41 couples were assessed at home, where two of the couples also received counseling sessions. The overall dropout rate of 19.5 percent (eight of 41 couples) is not uncommon in this population.

The intervention had a significant effect on well spouses’ evaluation of their relationship with their partners, as indicated by the Dyadic Adjustment Scale (DAS), a well-known scale that measures relationship quality. A significant improvement in the DAS occurred from baseline to the two-month follow-up for well spouses in the intervention group compared with
those in the control group. This was maintained at the four-month follow-up. A significant difference was also seen between the two groups in the Goal Attainment Scale, with both well spouses and people with Alzheimer’s disease in the intervention group more likely to have achieved their goals at the two-month follow-up than those in the control group. Couples in the intervention group also reported improved communication.

Study participants shared their appreciation with the staff for having had the opportunity to express thoughts and feelings they previously felt were too frightening or dangerous to convey to each other. They also expressed appreciation for discovering that the relationship could continue to support the integrity and value of each member despite the impact of the illness. While goals expressed at baseline were largely achieved, new goals emerged and were addressed during counseling. Most well spouses said they were surprised at how communicative their ill spouses were during the counseling sessions. Interestingly, after participating in the intervention, 11 of the men with Alzheimer’s disease joined an early-stage support group run by one of the counselors.

Results of this pilot study suggest that providing counseling to couples while the functional impact of the illness is still relatively mild can have a significant positive effect on their relationship. Results from this Zenith Fellows Award–supported study were published in two articles appearing in the peer-reviewed journal *Clinical Gerontologist*. The high level of satisfaction that participants expressed and the positive effects of the intervention on the marital relationship suggest that additional investigation of couples counseling is warranted.”

“I received a Zenith Fellows Award from the Alzheimer’s Association to systematically test, for the first time, the effectiveness of counseling for couples in which the husband or wife had early-stage Alzheimer’s disease. While couples counseling is an established therapeutic modality and clinicians may offer it in their practices, it had not been rigorously evaluated in this population.”

— MARY MITTELMAN, D.P.H.
Alzheimer’s disease is strongly linked to abnormal metabolism of beta-amyloid and its precursor, the amyloid precursor protein (APP). In addition to the 40- and 42-amino-acid-long forms of beta-amyloid, cerebrospinal fluid (CSF) and brain tissue contain a broad range of other beta-amyloid peptides. These beta-amyloid fragments result when enzymes called secretases clip APP. During the past year, we have confirmed earlier data suggesting that types of beta-amyloid fragments in CSF separate individuals with sporadic Alzheimer’s disease from those without Alzheimer’s with high accuracy. In addition to the well-established Alzheimer biomarker beta-amyloid 1-42, those with Alzheimer’s have high levels of the shorter fragment beta-amyloid 1-16, in CSF.

Experiments conducted in cell cultures and in mice show that this fragment is the result of alpha- and beta-secretase clipping the same APP molecule. This represents a previously unknown pathway in which APP is processed. We have recently verified this pathway in dogs. Further, we have shown that this pathway is strongly induced in response to the inhibition of the gamma-secretase enzyme in cell cultures, mice, dogs and humans. Since beta-amyloid 1-16 is water-soluble and not influenced by overall amounts of amyloid in the brain, we believe that this marker will be very useful in future studies of potential therapies that inhibit or change the behavior of gamma-secretase. We have also shown that beta-amyloid 1-16 does not have any acute toxic effect on synapses on its own.

When comparing the beta-amyloid patterns in the CSF of people with sporadic Alzheimer’s and those who are carriers of the Alzheimer’s-causing genetic mutation PSEN1 A431E, the patterns separate the two groups completely. PSEN1 A431E mutation carriers have levels of beta-amyloid 1-40 and 1-42 that are similar to people with sporadic Alzheimer’s, but mutation carriers have extremely low levels of beta-amyloid 1-37, 1-38 and 1-39. It is tempting to speculate that these fragments may inhibit the aggregation of individual beta-amyloid 1-42 peptides into multiple-peptide oligomers and that the key Alzheimer’s-promoting effect of PSEN1 A431E, and possibly several other familial Alzheimer’s disease–associated PSEN mutations, is gamma-secretase activity that results in loss of the protective beta-amyloid 1-37, 1-38 and 1-39 peptides. Modulating gamma-secretase function would in that case be a novel approach to prevent Alzheimer’s-associated beta-amyloid aggregation.
“The Alzheimer’s Association grant was a true vitamin injection into our ongoing research examining methods to better understand the origins of Alzheimer’s.”

— HENRIK ZETTERBERG, M.D., PH.D.

Finally, we have discovered several previously unknown N-terminal fragments of APP and APP/beta-amyloid fragments. The results described above have thus far resulted in five publications.

The Alzheimer’s Association grant was a true vitamin injection into our ongoing research examining methods to better understand the origins of Alzheimer’s. Some of these methods had been under development for quite a while. We realized their potential in shedding light on how amyloid metabolism might be changed in individuals with Alzheimer’s disease or those at high risk of developing Alzheimer’s and wrote a grant proposal describing how we would push the projects further. The reviewer comments were very positive and helpful, and the grant money was really needed. It is also notable that Alzheimer’s Association funding is quite prestigious and very well recognized in the field.”
“Funding from the Alzheimer’s Association has helped advance my career in Alzheimer’s disease research on multiple fronts. First, funding from the Alzheimer’s Association has allowed us to determine that magnetic resonance imaging (MRI) can be used to detect the accumulation of gangliosides (a type of lipid associated with beta-amyloid) before the symptoms and behavioral changes of the disease develop. A paper describing the results of this work was accepted for publication in the journal *Magnetic Resonance in Medicine*, and the Alzheimer’s Association is gratefully acknowledged. Second, funding from the Association has allowed us to test new MRI contrast agents aimed at detecting the accumulation of protein and lipids in the brain, as well as molecules called ‘reactive oxygen species’ that include free radicals, and microglia, cells that normally protect neurons but that may malfunction in Alzheimer’s.

Support from the Alzheimer’s Association has also advanced my career through facilitation of collaborations and interactions with other scientists. For example, funding from the Alzheimer’s Association to Dr. Eric Klann helped foster a collaboration between my lab and Dr. Klann’s lab at New York University. As a result, we co-mentored a post-doctoral researcher whose findings will appear in the prestigious *Proceedings of the National Academy of Sciences*. Additionally, the findings from our collaboration helped this young post-doc obtain independent research funding, which she will use as a springboard to launch her own career.
More than words can say, I am extremely grateful to the Alzheimer’s Association for its grant support, the introduction to many other scientists and members of the public, and for helping facilitate productive collaborations.

—— ROBIA PAUTLER, PH.D.

I’ve also benefited from my local Alzheimer’s Association chapter in Houston and the Association’s national office, which have helped introduce me to many other scientists as well as members of the public. This combination of scientific and lay perspectives has had a tremendous impact on me professionally and personally.

More than words can say, I am extremely grateful to the Alzheimer’s Association for its grant support, the introduction to many other scientists and members of the public, and for helping facilitate productive collaborations.”
"My interest in understanding the molecular and cellular events underlying the demise of nerve cells in the healthy or debilitated brain as it ages has been lifelong. Formally, it began during my graduate training at the Institute of Pharmacology of the University of Rome 'La Sapienza' in Italy. I still remember the words from my mentor that set the stage for my scientific career, from my postdoctoral years spent on both sides of the Atlantic Ocean in the United States and Italy, to my current position as a tenured associate professor in the Department of Neuroscience and Cell Biology at the University of Texas Medical Branch at Galveston. On one of those long-ago Roman days, I was excitedly reporting about an experiment we had conducted in which the lifespans of extremely old (and rather debilitated) laboratory animals were extended. My mentor quickly dampened my enthusiasm with a grave look and a sage warning: 'Why add years to later life, rather than add life to later years?'

This simple notion elegantly describes the challenge faced by hundreds of scientists through several decades of research for a cure for Alzheimer’s disease. Indeed, the most devastating aspect of Alzheimer’s is the individual’s gradual loss of cognitive function, slowly chipping away at the faces, places and memories familiar to them. No one knows if halting or even reversing this cognitive decline may extend the individual’s life, but certainly it would be a formidable step toward assuring quality life in one’s later years.

With this goal in mind, my research focuses on identifying mechanisms of nerve cell malfunction in the early stages of Alzheimer’s that are responsible for the initial changes in mental function. The hope is that once detrimental processes are identified, they could be corrected with medications.

Perhaps the best characterized physical feature of brains afflicted with Alzheimer’s disease is the conspicuous presence of amyloid plaques formed by aggregates (fibrils) of individual units of the protein beta-amyloid. Although recognized for many years as a hallmark of Alzheimer’s, it was found that the number of amyloid plaques on autopsy in individuals with Alzheimer’s did not correlate with the disease severity. Instead, the levels of much smaller aggregates of beta-amyloid (oligomers) that precede the development of large fibrils and plaque formation were directly associated with disease severity. This indicated that beta-amyloid oligomers rather than later-formed fibrils may be the main offender in Alzheimer’s disease. Significantly, other studies found that beta-amyloid oligomers injected directly into the brains of healthy laboratory rodents produced severe memory deficits without inducing the death of brain cells, thus suggesting that beta-amyloid oligomers may trigger cognitive impairment through disturbing neuron function. As such, their effect on memory may be reversible if the cellular mechanisms involved are better understood.
“[O]urs] was an ambitious plan, but bore the potential for returning highly significant results if successful. In other words, this project could only be funded by an organization that would take a calculated risk to support a novel idea. And that is why we turned our attention and hope to the research grants program of the Alzheimer’s Association.”

— GIULIO TAGLIALATELA, PH.D.

While these seminal observations sparked a wealth of research aimed at characterizing beta-amyloid oligomers, we discovered that the levels of calcineurin, an enzyme that impedes memory formation, were elevated in the brains of mice genetically altered to produce human beta-amyloid. Elevated levels of calcineurin, the appearance of beta-amyloid oligomers, and memory deficits were present simultaneously in these mice, but months before the appearance of amyloid plaques. Most important, when we treated these cognitively impaired mice with a drug that inhibits calcineurin, their memory was restored. Could that indicate that calcineurin initiated the memory deficits associated with beta-amyloid oligomers in these genetically altered mice? And if so, could drugs that inhibit calcineurin stop or reverse this process?

Our initial results using artificial beta-amyloid oligomers published in 2008 in the journal Aging Cell were highly encouraging and suggested that calcineurin inhibition should be further explored as a way to alleviate cognitive impairment in the early stages of Alzheimer’s. However, proof that the presence of beta-amyloid oligomers in the brain caused calcineurin-induced memory changes was needed to push this particular field forward. One way to achieve this goal was to extract beta-amyloid oligomers directly from the brains of genetically altered mice, inject them into the brains of normal mice, and observe if 1) this resulted in elevated levels of calcineurin in the brain, 2) memory was impaired and 3) treatment with a calcineurin inhibitor would reverse these effects. This was an ambitious plan, but bore the potential for returning highly significant results if successful. In other words, this project could only be funded by an organization that would take a calculated risk to support a novel idea. And that is why we turned our attention and hope to the research grants program of the Alzheimer’s Association.

To our excitement, although not entirely surprisingly considering the long-standing track record of the Alzheimer’s Association for supporting the development of innovative research, our grant application was funded in July 2008. Experimental work begun shortly thereafter, only to be abruptly stopped on September 13th, 2008, when Hurricane Ike hit Galveston Island and our campus with unprecedented devastating force. Surging sea waters inundated the first floor of every single campus building and dramatically disrupted access to our genetically altered mice. This compromised our ability to extract beta-amyloid oligomers from these mice to test our newly funded project. However, sometimes disasters can change things for the better in unexpected ways.

In August 2008 an influential paper was published in the journal Science by the group led by Dr. Dennis Selkoe at Harvard Medical School. This work illustrated that beta-amyloid oligomers extracted directly from autopsied brain tissue disturbed electrical activity in neurons and disrupted memory when injected into the brains of laboratory animals. While these authors did not specifically address the mechanism involved, their results fit our hypothesis and previous rodent data like a glove on one’s hand.
Indeed, calcineurin has been known for many years to be intimately involved in regulating neuron electrical activity (the cellular basis of memory) and memory itself. Dr. Selkoe’s work further suggested to us that we could probably take a leap forward and directly test human (instead of mouse) beta-amyloid oligomers for their ability to activate calcineurin and produce memory changes that could be prevented or reversed by treatment with calcineurin inhibitors. A lack of access to our mouse colony proved to be a silver lining of Hurricane Ike’s clouds, as we shifted our focus to the mechanisms of Alzheimer’s disease in human rather than mouse models.

As a result of this new exciting evidence, and supported through the difficult months following the storm by the long-sighted generosity of the Alzheimer’s Association, we secured a steady supply of Alzheimer brain samples from two reputable national brain banks and began isolating the infamous beta-amyloid oligomers. We also performed a wealth of biochemical analyses on these human brains that revealed signs of calcineurin over-activation similar to what we observed in the brains of genetically altered mice that express human beta-amyloid. This suggested that our hypothesis regarding what happens when beta-amyloid oligomers are present to cause toxic effects on neurons may be on target and that the elevated levels of calcineurin we found may in fact play a role in the disease.

Strengthened by these additional results, during the next two years of support by the Alzheimer’s Association we plan to complete our studies exclusively using purified human beta-amyloid oligomers. More important, we truly hope that achieving the goals of this project will thrust forward the novel concept of inhibition of calcineurin as a strategy to slow or halt the disruption of cognitive function in people with early to mid-stage Alzheimer’s disease.”
The hardest part of caring for loved ones with Alzheimer’s disease is not the everyday practical challenge, but rather the emotional impact of losing the support and companionship of the loved one, according to research conducted at the University of Indianapolis. “The fundamental barrier experienced by Alzheimer’s caregivers appears to be a combination of anticipatory grief and ambiguous loss, rather than hands-on care issues,” said researcher Jacquelyn Frank, Ph.D. "Alzheimer’s Care: Grief is Heaviest Burden for Caregivers"

According to researchers, individuals who experience a stroke and have the apolipoprotein E (APOE) e-4 gene have a greater risk of dementia than individuals with just one—or none—of these factors. "Gene Mutation Plus Stroke Increases Dementia Risk"

Study results indicated that non-steroidal anti-inflammatory drugs (NSAIDs) can reduce the risk of various forms of dementia in older adults. However, only those with the APOE-e4 gene had a reduced risk of developing Alzheimer’s. These findings provide clues for studies of the underlying biology of dementia and Alzheimer’s disease. "NSAIDs Associated with Lower Risk of Dementia, Study Suggests"

Studies of the developing brain gave scientists another important clue to why nerve cells die in neurodegenerative diseases. The studies revealed that a baby’s brain generates roughly double the number of nerve cells it needs to function, with cells that receive both chemical and electrical stimuli from other cells surviving, and the remaining cells dying. "Use It or Lose It” Theory Gains Ground"
10

Lipids Reverse Plaque Formation
Researchers discovered that naturally occurring lipids found throughout the brain can dissolve the large insoluble protein plaques characteristic of Alzheimer’s disease, releasing their smaller soluble components. This showed that, in a mouse model of Alzheimer’s, plaque formation is reversible. These smaller soluble components may be a new target for disease intervention.


People Live An Average of 4.5 Years After Dementia Diagnosis
People with dementia survive an average of four-and-a-half years after diagnosis, researchers learned after studying 13,000 people aged 65 or older with the condition between 1991 and 2005. Age, gender and disability were the main factors determining how long a person survived. Women lived for 4.6 years compared with 4.1 years for men, and people aged 65 to 69 lived 10.7 years compared with those over 90, who lived only 3.8 years. The findings might help policy makers, families and health professionals better plan and care for people with dementia.

*British Medical Journal* online (Print: February 2, 2008;336(7638):258–262.)

16

Cholesterol Drugs Don’t Protect Against Alzheimer’s
Autopies of brains from 262 individuals failed to show an association between statin use and reduced levels of Alzheimer’s-related brain changes. However, because relatively few of the those in the study used statins, the researchers conclude that further studies, possibly incorporating sophisticated brain imaging tests, will be needed to verify these results.

*Neurology* online (Print: May 6, 2008;70(19):1795–1802.)

Diabetes Plus Alzheimer’s Gene Ups Dementia Risk
Among individuals who carry the APOE-e4 gene associated with an increased risk of Alzheimer’s disease, the risk of dementia is further increased for those who also have diabetes. Among the 2,547 study volunteers, the 253 volunteers who had diabetes alone at the start of the study had a 62 percent higher risk of developing Alzheimer’s disease. The 67 participants with both diabetes and APOE e-4 at the start of the study had a 2.5-fold risk of developing Alzheimer’s. The authors suggest that high blood sugar levels or reduced blood flow to the brain may increase the production or deposition of beta-amyloid and that large- and small-vessel damage in the brain caused by diabetes may impede the clearance of beta-amyloid.


17

Tau Regulates Protein Movement in Neurons
Researchers discovered that proteins carrying chemicals in nerve cells react differently when exposed to the tau protein, which is implicated in the development of Alzheimer’s disease. The proteins dynein and kinesin transport chemicals toward opposite ends of tracks called microtubules. Tau binds to the microtubule surface and acts like a speed bump to regulate protein traffic. These findings show a mechanism of regulating the transport of nutrients, signaling molecules and waste proteins along a nerve cell’s axon. Neurodegenerative diseases such as Alzheimer’s may arise when pieces of this shipping system go awry.

*Science* online (Print: February 22, 2008;319(5866):1086–1089.)
18

Altering Brain’s Lipid Metabolism Reduces Alzheimer Plaques in Mice
Researchers learned that elevated levels of the protein ABCA1 sharply reduced buildup of beta-amyloid plaques in the brain in mice, potentially slowing the development of Alzheimer’s disease. ABCA1 helps the brain use cholesterol. The study raises the possibility of treating Alzheimer’s by altering the brain’s use of lipids, a class of compounds that includes cholesterol. Journal of Clinical Investigation online (Print: February 1, 2008;118(2):671–682.)

19

Enzyme Regulates Blood Flow to Neurons
Research revealed that the human brain contains its own store of the enzyme (and stroke drug) tissue plasminogen activator (tPA), which appears to help regulate blood flow to brain cells. Scientists found that this natural tPA boosts blood flow to brain cells via its influence on nitric oxide (NO) synthase, which is essential to the production of nitric oxide. NO widens blood vessels and improves blood flow to neurons as they become more active. The new findings could have implications for the study of stroke and Alzheimer’s disease, which are both associated with marked declines in natural brain levels of tPA. Proceedings of the National Academy of Sciences online (Print: January 22, 2008;105(3):1073–1078.)

19

Less Education May Lead to Delayed Awareness of Alzheimer Onset
Older adults with more education and higher levels of occupational achievement are better able to weather loss of brain volume, and even Alzheimer’s disease pathology, without showing signs of dementia, say researchers. Researchers also report that highly educated individuals who develop Alzheimer’s are likely to be diagnosed at a younger age. They suspect that people who spend fewer years in school may experience a slight but statistically significant delay in the realization that they’re having cognitive problems that could be Alzheimer’s disease, and therefore, seek treatment later in the disease process. Archives of Neurology, January 2008;65(1):113–120.

23

Study Examines Driving Skills Among People with Alzheimer’s Disease
A study confirmed that people with early Alzheimer’s disease were involved in more traffic accidents and performed worse on road tests than drivers without cognitive impairment. The study also showed that some people with mild dementia are able to continue driving safely. The study results suggest that regular driving assessments may reduce the frequency of motor vehicle accidents among drivers with mild dementia by increasing awareness of driving ability among affected individuals and their caregivers. Neurology online (Print: April 1, 2008;70(14):1171–1178.)

29

Phase II Study of Dimebon Accepted as a Pivotal Study
The maker of the experimental Alzheimer drug Dimebon received regulatory sign-off to conduct a single phase III trial study. The U.S. Food and Drug Administration agreed to accept a previously completed phase II study of Dimebon conducted in Russia as one of the two pivotal studies required to support the drug’s approval to treat Alzheimer’s disease. The data from the phase II study supported the benefits of Dimebon, but were controversial because not everyone believes the results could be replicated in the United States or Europe. www.thestreet.com
31

**Functional MRI Aids Understanding of Memory Loss**

A functional MRI study showed how two regions of the brain affected by Alzheimer’s disease—the hippocampus and medial parietal lobes—cooperate to form new memories and gave researchers a look at what goes wrong during aging-related memory loss. Functional imaging can help researchers understand whether the presence of amyloid is the beginning of Alzheimer’s and whether intervention should occur at that early point.

*Proceedings of the National Academy of Sciences* online (Print: February 12, 2008;105(6):2181–2186.)

---

February

1

**Phase II Trial of Huperzine A in Alzheimer’s Disease Fails**

A phase II clinical trial of Huperzine A in individuals with mild-to-moderate Alzheimer’s disease did not meet its primary endpoint. The results showed no statistical difference in the mean change on the Alzheimer’s Disease Assessment Scale–Cognitive scores scale, the primary endpoint of the study, after 16 weeks’ treatment with 200 micrograms of Huperzine A compared with placebo.

*RTTNews*

3

**Discipline and Alzheimer’s Disease**

People who have a tendency to be self-disciplined, careful and purposeful appear less likely to develop Alzheimer’s disease. Research suggested that conscientious people may be more likely to be successful academically and in their professions, both of which have been associated with a reduced risk of Alzheimer’s disease.


**Antioxidant Vitamin Supplement Use and Risk of Alzheimer’s**

Supplemental vitamin E and C, used alone or in combination, did not reduce the risk of Alzheimer’s disease or overall dementia during 5.5 years of follow-up. Evidence from several large, randomized control trials suggests that antioxidant supplementation does not maintain cognitive performance in cognitively intact individuals or delay Alzheimer’s in those with mild cognitive impairment.


5

**Folate Deficiency Associated with Tripling of Dementia Risk**

Folate deficiency is associated with a tripling of the risk of developing dementia among elderly people, said researchers. The onset of dementia was significantly more likely in those whose folate levels decreased over two years while their homocysteine levels rose. People who were folate deficient at the beginning of the study were almost 3.5 times more likely to develop dementia than those who were not.

*Journal of Neurology, Neurosurgery and Psychiatry* online (Print: August 2008;79:864–868.)
Intranasal Insulin Improves Memory in Early Alzheimer’s Disease
Daily intranasal insulin treatment improves cognition and functional status in individuals with early Alzheimer’s disease and amnestic mild cognitive impairment, results of a pilot study showed. Insulin is a key neuromodulator in the central nervous system, but levels of insulin and its signaling molecules are reduced in the central nervous system of those with Alzheimer’s disease. Researchers theorized that achieving normalized brain insulin levels would help restore brain function.

Alzheimer’s Plaques Can Form in One Day
An advanced imaging study has captured the fact that amyloid plaques, harbingers of Alzheimer’s disease, can develop in just 24 hours. The studies showed that nerve cell changes associated with Alzheimer’s disease appear within days after the formation of plaques.

Those with Mild Alzheimer’s Disease Show Rapid Decline in Financial Skills
Research showed that those with mild Alzheimer’s disease experience a dramatic decline over a one-year period in their ability to make financial decisions. This is accompanied by declines in basic judgment and monetary calculation skills. The findings underscore the importance of financial planning and transfer of financial responsibilities soon after diagnosis.
American Journal of Geriatric Psychiatry online (Print: August 2008;16(8):650–659.)

Most are Unaware of Heart Health, Dementia Link
A survey conducted by the Alzheimer’s Association and the American Heart Association of more than 2,000 people nationwide, including 1,210 African-Americans, showed most don’t know about the connection between cardiovascular conditions and the risk for dementia. Only 8 percent of African-Americans surveyed realized that cardiovascular conditions put them at an elevated risk of dementia.
USA Today, February 11, 2008 (http://www.alz.org/news_and_events_12875.asp)

Protein May Protect Against Alzheimer’s Disease
Scientists reported that the protein transthyretin (TTR) could be a natural defense against Alzheimer’s disease in humans and that this defense diminishes as people age. The findings suggest that TTR binds beta-amyloid in a manner that prevents both toxicity and plaque formation, presumably by interfering with the aggregation of the kinds of beta-amyloid that are most likely to stick together and cause neurological and behavioral deficits in experimental mice. If so, TTR–based therapy might help treat or prevent Alzheimer’s.
Proceedings of the National Academy of Sciences online (Print: February 19, 2008;105(7):2681–2686.)
Scientists Develop Tool to Probe Role of Oxidative Stress in Aging and Disease
University of Michigan researchers reported a new method to observe how oxidative stress affects the major building blocks of a cell: proteins. The new technique, called OxiCAT, enables measurement of the oxidative state of thousands of different proteins in a single experiment. Such insights might lead to the development of anti-oxidant strategies for combating Alzheimer’s.

Proceedings of the National Academy of Sciences, online (Print: June 17, 2008;105(24):8197–8202.)

Evidence Found for Genes that Affect Risk of Developing Alzheimer’s Disease
Through one of the largest familial studies yet of Alzheimer’s disease, researchers found strong evidence that genes other than the well-known susceptibility risk factor gene APOE-e4 influence who is at risk for developing Alzheimer’s later in life. Studying 25 multigenerational families of individuals diagnosed with late-onset Alzheimer’s disease (LOAD), as well as hundreds of other participants, the researchers found that blood levels of beta-amyloid proteins associated with Alzheimer’s were significantly elevated in blood relatives of those with Alzheimer’s compared with protein levels in non-blood relatives such as spouses. These results suggest that genetic factors lead to significant elevations of beta-amyloid in the blood of asymptomatic, young individuals from extended LOAD families.


Memory Loss Declining Among U.S. Seniors
Older Americans are having less trouble with their memories, according to one study, and it may be because they spent more time in school. Researchers found the rate of cognitive impairment—which includes a range of ills from significant memory loss to Alzheimer’s disease—fell 3.5 percentage points among people 70 and over between 1993 and 2002. The research reinforces other studies that suggest people who do mentally challenging tasks early on build up a reserve of brain power that helps them withstand later injuries to the brain.


Beta-Amyloid Levels in Plasma Predict Alzheimer’s Disease Risk in Elderly Men
Levels of beta-amyloid protein in plasma predict the risk of Alzheimer’s disease in elderly men, said a group of researchers. Low plasma beta-amyloid 1-40 levels in 77-year-old men were associated with a higher incidence of Alzheimer’s.


Cancer-Related Protein May Play Key Role in Alzheimer’s Disease
Researchers reported that increased amounts of the cancer-related protein Akt may prevent the removal of abnormal proteins, such as tau, causing them to accumulate and disrupt cells. Accumulated tau forms the bundles of tangled nerve cell fibers in the brain that are associated with Alzheimer’s disease. Regulating Akt levels may prove beneficial in treating Alzheimer’s. This research was funded in part by the Alzheimer’s Association.

Proceedings of the National Academy of Sciences online (Print: March 4, 2008;105(9):3622–3627.)
**22**

**Computers May Offer Breakthrough in Alzheimer Diagnosis**

Computer software can diagnose Alzheimer’s disease from brain scans more reliably than clinical experts, according to one study. The software studied learned the difference between the MRI brain scans of those with Alzheimer’s and those without the disease and had an accuracy rate as high as 96 percent. *Brain*, March 2008;131(3):681–689.

**25**

**Antibiotics Frequently Given to Individuals with Advanced Dementia**

A study found that people with advanced dementia are frequently given antibiotics toward the end of life. The study raises the question of whether this practice should be curtailed in view of the increased risk of individuals developing drug-resistant superbugs. Those with advanced dementia who are living in nursing homes are at high risk of infections and antimicrobial exposure near the end of life. Researchers suggest that the implications of this practice be evaluated with respect to individual treatment burden near the end of life and its contribution to the emergence of antimicrobial resistance in nursing homes. *Archives of Internal Medicine*, April 2008;168(4):357–362.

**27**

**Role for Ginkgo Biloba in Memory Decline is Unclear**

Taking the supplement ginkgo biloba had no clear-cut benefit in reducing the risk of memory problems, according to a study. Although data suggested a trend favoring ginkgo, the difference between those who took ginkgo versus placebo was not statistically significant. Further studies are needed to determine whether ginkgo biloba has any benefits in preventing cognitive decline and whether it is safe. *Neurology* online (Print: May 6, 2008(19);70:1809–1817.)

**28**

**Immunoglobulin Treatment is Associated with a Reduced Risk of Alzheimer’s Disease**

The risk of developing Alzheimer’s disease may be reduced by about 40 percent in those previously treated with intravenous immunoglobulin (IVIg). IVIg—an antibody product derived from human plasma and FDA-approved to treat other conditions, but not Alzheimer’s—has been found to contain antibodies that bind to beta-amyloid proteins. Earlier clinical studies evaluating IVIg in individuals with Alzheimer’s suggested that it may improve cognitive function. *10th International Hong Kong/Springfield Pan-Asian Symposium on Advances in Alzheimer Therapy*

**March**

**5**

**Dementia Diagnosis Brings Relief, Not Depression**

A study found that 69 percent of those who eventually received a diagnosis of Alzheimer’s disease had no significant changes in depression and that anxiety among individuals with Alzheimer’s and their caregivers decreased substantially. “The major finding is that both patients and their families feel relief, not increased anxiety, upon learning the diagnosis,” said the study author. *Journal of the American Geriatrics Society*, March 2008;56(3):405–412.
7

**FDG-PET Imaging May Lead To Earlier Diagnosis of Dementia**
Researchers involved in a large, multi-institutional study using PET imaging with the radiotracer fluoro-deoxyglucose (FDG) classified different types of dementia with high rates of success, raising hopes that dementia diagnoses may one day be made at earlier stages. The overall accuracy among dementias was 96 percent.

10

**Having Two Parents with Alzheimer's Further Raises Child's Risk**
If both parents have Alzheimer's disease, their children face an increased risk of developing the condition, a new study suggests. Forty-two percent of offspring whose parents both had Alzheimer's went on to develop the disease themselves by age 70, researchers found. Having one parent with Alzheimer's increases one's risk of developing the disease, but having two parents with the disease increases it even further. The risk is greater of developing the disease early if additional relatives have Alzheimer's disease, researchers said.

12

**Study Confirms Role for PET-PiB**
A study conducted by University of Pittsburgh researchers confirms that Pittsburgh compound-B (PiB) binds to the telltale beta-amyloid deposits found in the brains of individuals with Alzheimer's disease. The finding is a significant step toward enabling clinicians to provide a definitive diagnosis of Alzheimer's disease in living individuals. PiB is a radioactive compound injected into the bloodstream that, when coupled with positron emission tomography (PET) imaging, can enable researchers to identify the location and distribution of the beta-amyloid plaque deposits associated with Alzheimer's.
*Brain* online (Print: June 2008;131(6):1630–1645.)

13

**Link Between Alzheimer's and Stroke Illuminated**
Although scientists have known that the risk of Alzheimer’s disease is nearly doubled among people who have had a stroke, the source of the relationship has been obscure. Now researchers have found that the production of beta-amyloid, a hallmark of Alzheimer’s, increases after a stroke.

25

**Explanation Proposed for Diabetes-Alzheimer's Link**
Individuals with diabetes have a significantly higher risk of developing Alzheimer's disease but the molecular connection between the two has remained unexplained. However, investigators exploring the link reported that blood vessels in the brains of young diabetic mice are damaged by the interaction of elevated blood glucose levels characteristic of diabetes and low blood levels of beta-amyloid, a protein that clumps to form the senile plaques that riddle the brains of individuals with Alzheimer's.
*Neurobiology of Aging*, online only
Larger Belly in Mid-Life Increases Risk of Dementia
People with larger bellies in their 40s are more likely to have dementia when they reach their 70s. A study found that those with the highest amount of abdominal fat were nearly three times more likely to develop dementia than those with the lowest amount of abdominal fat. *Neurology* online (Print: September 30, 2008;71(14):1057–1064.)

Brain Imaging Model Distinguishes Alzheimer’s Disease from Other Types of Dementia
A computer-assisted imaging technique that measures sugar metabolism in a critical area of the brain could hold a key to the early diagnosis of Alzheimer’s disease and other dementias. Researchers say that the technique was 94 percent accurate in distinguishing Alzheimer’s disease from other dementias. *Journal of Nuclear Medicine*, March 2008;49(3):390–398.

April

1. Whites with Alzheimer’s Disease Fare Worse
Whites with Alzheimer’s disease die sooner than their African-American and Latino counterparts, according to data obtained from more than 30 U.S. Alzheimer’s Disease Centers. Reasons for this difference may include disease management, genetic factors and cultural factors. During an average follow-up of about 2-1/2 years, 41 percent of whites died. Native Americans had the next highest mortality rate at 38 percent, followed by African-Americans at 30 percent, Latinos at 21 percent and Asians at 17 percent. *Neurology*, April 1, 2008;70(14):1163–1170.

2. Antipsychotic Drugs of Little Benefit to Those with Alzheimer’s
The continued use of antipsychotic drugs provides no cognitive or neuropsychiatric benefit for individuals with Alzheimer’s, a British study concluded. Study participants were divided into two groups—one continued treatment with the drugs, while the other group stopped treatment. Individuals were assessed six and 12 months later, and the researchers found no differences between the two groups in terms of cognitive decline or the number of neuropsychiatric problems. *Public Library of Science Medicine*, April 2008;5(4):e76.

8. Depression Increases Risk of Alzheimer’s Disease
People who have been diagnosed with depression are 2.5 times more likely to develop Alzheimer’s disease than people who have never had depression, according to researchers. Those who experienced depression before age 60 were nearly four times more likely to develop Alzheimer’s than those with no depression. *Neurology*, April 8, 2008;70(15):1258–1264.
9

**Diabetes in Mid-Life Linked to Increased Risk of Alzheimer’s Disease**

Men who develop diabetes in mid-life appear to have a significantly increased risk of developing Alzheimer’s disease, said researchers. They found that the men with low insulin levels at age 50 were nearly one-and-a-half times more likely to develop Alzheimer’s disease than those without reduced insulin levels. The risk remained significant regardless of blood pressure, cholesterol, body mass index and education.

*Neurology* online (Print: September 30, 2008;71(14):1065–1071.)

10

**How Beta-Amyloid Accumulates in Alzheimer’s Disease**

Researchers have identified a key mechanism by which beta-amyloid accumulates in Alzheimer’s disease. Researchers showed that endocytosis—the process by which the outer membrane of a cell folds inward toward the cell center and enables material outside the cell to enter the cell—transports amyloid precursor protein into the cell, where it could go on to be cleaved by beta- and gamma-secretase to create the beta-amyloid that is a hallmark of Alzheimer’s. When researchers inhibited endocytosis in the brain cells of mice, beta-amyloid levels decreased. These findings have implications for the brain changes associated with Alzheimer’s and may provide insights into potential therapies to intervene in the development of Alzheimer’s.


15

**Most Early-Onset Dementia Not Alzheimer’s**

The root cause of early-onset dementia is usually not Alzheimer’s, but rather another neurodegenerative or autoimmune disorder, research suggested. Among individuals younger than 45, dementia is more likely related to conditions such as multiple sclerosis, Huntington’s, lupus or HIV infection.

*American Academy of Neurology Annual Meeting*

**High Doses of Vitamin E Associated with Longer Life in Individuals with Alzheimer’s**

People with Alzheimer’s who consume very high levels of vitamin E seem to live longer than those who do not, research suggested. Researchers found that those who consumed 2,000 international units of vitamin E daily lived 26 percent longer than those who did not.

*American Academy of Neurology Annual Meeting*

16

**Exercise Could Cut Risk of Mild Cognitive Impairment**

Regular physical exercise may help protect against mild cognitive impairment, according to a Mayo Clinic study. Moderate physical exercise between ages 50 and 65 was associated with a reduced risk of cognitive impairment. Researchers speculate that exercise may stimulate chemicals that protect brain cells or that exercise is a marker for an overall healthy lifestyle.

*American Academy of Neurology Annual Meeting*
Results from Largest Statin Study of Individuals with Alzheimer’s Disease Show Lipitor Has No Significant Impact on Disease
In a study of those with mild-to-moderate Alzheimer’s disease, the addition of Lipitor® to Aricept® resulted in no significant differences in cognition or overall function compared with placebo and Aricept. *American Academy of Neurology Annual Meeting*

Antipsychotic Drugs Increase Risk of Developing Pneumonia in Elderly, Study Suggests
Elderly individuals who use antipsychotic drugs have a 60 percent increased risk of developing pneumonia compared with non-users, said researchers. This risk is highest in the first week after beginning antipsychotic drugs and decreases gradually thereafter. Antipsychotic drugs are frequently given to treat behavioral problems associated with dementia. *Journal of the American Geriatrics Society*, April 2008;56(4):661–666.

Dimebon Significantly Improves Thinking and Memory in Individuals with Alzheimer’s
Those with Alzheimer’s disease who were treated with the investigational drug Dimebon showed improvement in key aspects of cognitive function over one year compared with individuals receiving placebo. Improvements occurred not only in memory and language, but also in functions such as awareness of time and place and praxis—the process of getting an idea and initiating and completing a new motor task. *American Academy of Neurology Annual Meeting*

Smoking, Drinking and Alzheimer’s Risk
Researchers reported that people who have more than two drinks per day developed Alzheimer’s disease almost five years earlier than lighter drinkers, on average. Heavy smokers (a pack of cigarettes or more per day) developed it 2–3 years earlier. Both smoking and drinking can damage cells and synapses in the brain, explained the researchers. *American Academy of Neurology Annual Meeting*

Cognitive Abilities Ease Impact of Alzheimer Pathology
Mental processing resources, such as perceptual speed and working memory, can reduce the effect of Alzheimer pathology on other cognitive abilities. Results of one study showed that people with stronger processing resources performed better in other cognitive areas despite the burden of Alzheimer pathology. *Neurology*, April 22, 2008;70(17):1534–1542.

Study Sheds New Light on Alzheimer’s Development
Scientists found a molecular link between Alzheimer’s disease and the development of beta-amyloid plaques. Researchers studied microRNAs (miR), short pieces of RNA that regulate protein production. Those with increased levels of the protein beta-secretase had significantly reduced levels of miR-29a and miR-29b-1. Beta-secretase plays a key role in the production of the beta-amyloid protein that is a hallmark of Alzheimer’s. The loss of specific miRNAs may contribute to increased levels of beta-secretase and beta-amyloid in late-onset Alzheimer’s, said scientists. *Proceedings of the National Academy of Sciences* online (Print: April 29, 2008;105(17):6415–6420.)
30

Experimental Drug Eases Symptoms of Mild Alzheimer’s

A British study concluded that people with mild Alzheimer’s disease who took 800 milligrams of the drug tarenflurbil (Flurizan®) twice a day had less decline in functional ability than those who took a placebo. Those with mild Alzheimer’s who received the drug experienced a 46 percent slower decline in performing daily activities and a 36 percent slower decline in overall function after a year of treatment compared with those receiving a placebo. However, there was no significant effect on cognition. Tarenflurbil reduces production of beta-amyloid 1–42, which may initiate the brain damage characteristic of Alzheimer’s disease.

*The Lancet Neurology* online (Print: June 2008;7(6):483–493.)

Cortical Thickness Reflects Network Connectivity in Alzheimer’s

Building on earlier research suggesting that the thickness of the cerebral cortex (the gray matter that forms the outermost layer of the cerebrum) is similar in regions of the brain that function together (are functionally correlated), researchers suggest that these cortical similarities change when functional ability changes in conditions such as Alzheimer’s. The result is mismatched cortical thickness between regions that normally have similar thicknesses. Changes in thickness correlations throughout the cortex, which may occur in Alzheimer’s, could make the brain’s communication network vulnerable to disruption.


Families Shed Light on Possible Causative Gene for Alzheimer’s

The genetic profile of two large Georgia families with high rates of late-onset Alzheimer’s disease points to a gene that may cause the disease, researchers said. Genetic variations called single nucleotide polymorphisms, or SNPs, are common in DNA, but a particular pattern of SNPs was found in nine of 10 affected family members in the study. The genetic variation was in the TRPC4AP gene, part of a large family of genes that is believed to regulate calcium. Calcium is needed throughout the body but abnormal regulation of calcium levels can result in inflammation, nerve cell death and possibly plaque formation. The finding provides new directions for research and possibly new treatment targets.

*American Journal of Medical Genetics* online (Print: January 2009;150B(1):50–55.)

May

1

Risk Factors for Progression from Mild Cognitive Impairment to Alzheimer’s Disease May Be Gender-Specific

French researchers reported that men and women have different risk profiles for progression from mild cognitive impairment to Alzheimer’s disease. The principal factors for men in descending order were APOE-e4 allele, stroke, low level of education, difficulty in carrying out instrumental activities of daily living and age. In women, the principal risk factors were difficulties in instrumental activities of daily living, APOE-e4 allele, low level of education, subclinical depression, use of anticholinergic drugs and age.

6

Ibuprofen May Be Linked to Reduced Alzheimer’s Risk
People who use the painkiller ibuprofen regularly for five years may be less likely to develop Alzheimer’s disease as they age, a study suggested. People who used nonsteroidal anti-inflammatory drugs (NSAIDs) long-term had a 25 percent lower risk of developing Alzheimer’s. The benefit was more pronounced with specific NSAIDs. The risk of developing Alzheimer’s decreased the longer a person used ibuprofen, with those using the drug for five years being more than 40 percent less likely to develop the disease. But the findings don’t put to rest a debate about the preventive or therapeutic role for NSAIDs, which are associated with gastrointestinal side effects when taken long-term.

*Neurology,* May 6, 2008(19);70:1672–1677.

7

Beta-Amyloid Levels in Plasma Fail to Predict Alzheimer’s Disease
Levels of two beta-amyloid proteins—beta-amyloid 1-40 and beta-amyloid 1-42, both of which are important components of senile plaque—in plasma do not appear to be useful biomarkers for development of Alzheimer’s disease, according to one study. Investigators found no significant association between elevated plasma levels of beta-amyloid and Alzheimer’s disease.


8

Obesity Linked to Increased Risk of Dementia
Obesity can increase the risk of Alzheimer’s disease by up to 80 percent and vascular dementia by 73 percent, researchers found. Experts do not know exactly why obesity impacts on the risk of dementia, although the high blood pressure that is associated with obesity is thought to play a role.

*Obesity Reviews,* May 2008;9(3)204–218.

8

Flavonoids Reduce Beta-Amyloid Levels in Mouse Model of Alzheimer’s
Flavonoids, compounds found in many fruits and vegetables, may lessen the brain changes of Alzheimer’s disease, said researchers. In experiments with mice, flavonoids called luteolin and diosmin reduced levels of beta-amyloid, which forms the plaques that build up in the brains of those with Alzheimer’s disease.

*Journal of Cellular and Molecular Medicine* online (Print: March 2009;13(3):574–588.)

12

Older Persons with More Schooling Spend Fewer Years with Cognitive Loss
Those with at least a high school education live 2.5 years more without cognitive loss—including the effects of Alzheimer’s, Parkinson’s and dementia—but die sooner after the loss becomes apparent than those without a high school education.

14

Study Shows No Benefit of DHEA in Cognitive Function
A study including 110 healthy men and 115 healthy women aged 55–85 who received either daily 50 mg doses of DHEA or a placebo for one year found no evidence of a beneficial effect of DHEA supplements on cognitive function. Six cognitive function tests were administered at the beginning of the study and after 12 months. The lead author of the study concluded that DHEA supplements had no cognitive benefits in this study group.
Journal of the American Geriatrics Society online (Print: July 2008;56(7):1292–1298.)

Heart Surgery Not Linked to Cognitive Decline
People who’ve undergone coronary bypass surgery are sometimes noted to have some degree of mental impairment later on, but researchers reported that the surgery is not to blame. They found that the cognitive decline in such individuals is comparable to that in those with heart disease who have not undergone surgery. Individuals with coronary artery disease may also have some degree of vascular disease involving the brain, and this, in combination with normal age-related changes, may explain the mild late cognitive changes.

Molecule Stops Formation of Fibers Associated with Alzheimer’s
In test tube studies, the addition of the small molecule 4,5-dianilinophthalimide (DAPH) to a solution containing beta-amyloid fibers caused the fibers to stop growing. Abnormal beta-amyloid fibers are associated with Alzheimer’s disease. These results suggest that finding a way to stop the misfolding of proteins that leads to fiber formation may be one approach to developing new treatments for Alzheimer’s. This research was funded in part by the Alzheimer’s Association.
Proceedings of the National Academy of Sciences online (Print: May 20, 2008;105:7159–7164.)

June
1

Yale Researchers Clear up Alzheimer Plaques in Mice
Blocking a common immune system molecule, TGF-β (transforming growth factor), cleared up plaques associated with Alzheimer’s disease and enabled treated mice to recover some lost memory, Yale University researchers reported. The research team found that as much as 90 percent of plaque formation was prevented in the brains of mice. This research was funded in part by the Alzheimer’s Association.

2

Antipsychotics May Improve Psychiatric Symptoms in Alzheimer’s Disease
Psychiatric and behavioral symptoms associated with Alzheimer’s disease, such as anger, agitation, aggression and paranoid thoughts and ideas, may improve with the use of second-generation antipsychotic medications, a study found. Improvements were seen both in global measures and in measures of specific symptoms. In addition, the analysis indicated that particular symptoms may respond better to different second-generation antipsychotic medications.
The American Journal of Psychiatry online (Print: July 2008;165(7):844–854.)
4

**Exercise May Cut Risk of Dementia**
Exercising in middle age may help ward off dementia and Alzheimer’s disease decades later. In a study of more than 1,400 adults, those who were physically active during middle age were 52 percent less likely to develop dementia 21 years later than their sedentary counterparts. Their chance of developing Alzheimer’s disease was slashed even more, by 62 percent.
_American College of Sports Medicine Annual Meeting_

12

**Apolipoprotein E Facilitates Beta-Amyloid Clearance from the Brain**
Researchers reported that apolipoprotein E (APOE) helps remove soluble beta-amyloid from the brain, increases the breakdown of beta-amyloid in microglia and facilitates the breakdown of beta-amyloid by insulin-degrading enzyme. They also found that enhanced expression of a certain form of APOE through activation of liver X receptors stimulated the breakdown of beta-amyloid.

18

**Grape Seed Extract Reduces Plaque Formation in an Animal Study**
To explore the potential role of compounds known as polyphenols in the treatment of Alzheimer’s disease, researchers gave the compounds to mice genetically altered to develop Alzheimer’s disease. The mice received polyphenols, which are found in grape seed extract, before they showed symptoms of Alzheimer’s. After five months, when these mice typically show Alzheimer symptoms, the treated mice showed reduced cognitive decline compared with nontreated mice, as well as reduced beta-amyloid accumulation and plaque formation. Additional research is needed to learn whether the same effects would be found in humans. This research was funded in part by the Alzheimer’s Association.

30

**Flurizan Fails in Key Study**
_Reuters_

**Presenilins Linked to Calcium Activity in Neurons**
The cell membrane proteins called presenilins may help maintain neuronal health by regulating the activity of a key calcium pump in cells, reported researchers. These data support the idea that calcium mismanagement in neurons can influence the development of physical changes in the brain that are associated with Alzheimer’s.
July

1

**Questionnaire Spots Alzheimer’s Risk**
A new questionnaire may help in both diagnosing older adults with dementia and in identifying individuals who need help with daily living. The Everyday Cognition instrument consists of 39 questions to be answered by people who are very familiar with the abilities of the person with memory or function loss. The hope is that this instrument will be able to help identify very early on those people at increased risk for developing Alzheimer’s disease.

2

**Anti-inflammatory Drugs Do Not Improve Cognitive Function in Older Adults**
Researchers reported that the anti-inflammatory drugs naproxen and celecoxib do not appear to improve cognitive function in older adults with a family history of Alzheimer’s disease, and naproxen may have a slightly detrimental effect.

Are Men or Women More Likely to Have Dementia in Very Old Age?
In a population-based study of 911 men and women aged 90 and older, researchers found that the overall prevalence of dementia from all causes was higher in women than men. Prevalence increased with age after age 90, essentially doubling every 5 years, for women, but not for men. A lower prevalence of dementia was significantly associated with higher education in women but not in men.

‘Good’ Cholesterol May Lower Dementia Risk
Too little of one type of cholesterol has been linked by research to memory loss and Alzheimer’s disease. The relationship between levels of HDL, or “good,” and LDL, or “bad,” types of cholesterol is thought to be important in the development of other serious conditions such as heart disease and stroke. Higher levels of HDL, in particular, are believed to protect against damage to the blood supply caused by the narrowing of the arteries. Evidence also shows that “good” cholesterol can influence the laying down of the beta-amyloid plaques that are a distinctive feature in the brains of those with Alzheimer’s.

10

**Imaging Technique May Spot Early Alzheimer’s**
An automated system for measuring hippocampal volume with magnetic resonance imaging (MRI) can help doctors more accurately diagnose Alzheimer’s disease at an earlier stage, according to researchers. The automated process performed as well as the manual process and is much faster. Combined with other tests, the new automated MRI technique can contribute to a more accurate diagnosis of Alzheimer’s disease.
New Cut Point Detects Dementia Risk Among Highly Educated Older Adults
A different cutoff point on an existing mental function assessment—the mini-mental state examination—may more effectively assess the risk of dementia in highly educated older adults, according to a new study. The authors suggest that using this cut point may help facilitate early detection of dementia in highly educated individuals.
*Archives of Neurology*, 2008;65(7):963–967.

Biological Marker for Alzheimer’s Holds Promise for Earlier Diagnosis
Researchers found evidence that increases in the size of the brain ventricles are directly associated with cognitive impairment and Alzheimer’s disease. The research showed that the volume of the brain ventricles expands as surrounding tissue dies.
*Brain* online (Print: September 2008;131(9):2443–2454.)

Exercise May Prevent Brain Shrinkage in Early Alzheimer’s Disease
People with early-stage Alzheimer’s disease who were less physically fit had four times more brain shrinkage compared with normal older adults than those who were more physically fit, suggesting less brain shrinkage occurs in Alzheimer’s among those with higher fitness levels.
*Neurology*, July 15, 2008(3);71:210–216.

Plaque Vaccine Doesn’t Slow Alzheimer’s
The vaccine AN-1792, aimed at reducing beta-amyloid plaques in the brain, didn’t stave off Alzheimer’s disease, undercutting the theory that beta-amyloid plaques are the driving force of the debilitating disease. While immunization with beta-amyloid cleared the plaques, it didn’t help individuals live longer or slow the disease’s progression.

Biomarkers Identify Alzheimer’s Before Symptoms Appear
Researchers found that during Alzheimer’s earliest stages, levels of specific proteins in the blood and spinal fluid begin to drop as the disease progresses, making them potentially useful as biomarkers to identify and track progression of Alzheimer’s long before symptoms appear. Identifying individuals at this silent stage is critical to developing treatments to prevent symptoms from appearing.

Using Multiple Imaging Methods Proves Valuable in Assessing Cognitive Function
Two Mayo Clinic studies found that imaging methods including magnetic resonance imaging, magnetic resonance spectroscopy, and positron emission tomography with 11C Pittsburgh Compound B each provide independently valuable information about cognitive function. By using all of these imaging methods together, the researchers say physicians can better predict the likelihood of an individual’s developing Alzheimer’s disease.
*Alzheimer’s Association International Conference on Alzheimer’s Disease*
28

Drug Boosts Memory in Individuals with Mild Cognitive Impairment
A nasal spray made by Allon Therapeutics Inc. significantly improved some measures of memory in people with mild cognitive impairment, a potential precursor to Alzheimer’s disease. The drug, AL-108, was among the first of a new class of Alzheimer’s treatments to target the fibrous tangles in the brain caused by an abnormal build-up of the protein tau.

Alzheimer’s Association International Conference on Alzheimer’s Disease

Dual Diabetes Drugs Help Stave Off Alzheimer’s
People with adult-onset diabetes who take insulin plus a diabetes pill have a lower risk of developing Alzheimer’s disease than diabetics who take insulin alone, reported researchers. Those who were treated with both insulin and a diabetes pill had 80 percent fewer beta-amyloid plaques than those not receiving dual treatment. Beta-amyloid plaques are a characteristic feature of Alzheimer’s disease. The finding may help lower the risk of Alzheimer’s disease in individuals with diabetes.

Alzheimer’s Association International Conference on Alzheimer’s Disease

29

Drug Improves Brain Function and Reduces Levels of a Key Alzheimer Protein
The drug PBT2 was shown to improve the brain function of people with early-stage Alzheimer’s disease and reduce levels of a key protein in spinal fluid that is associated with the disease. The drug counteracts the production and accumulation of the protein beta-amyloid that occurs in Alzheimer’s disease. This protein, which clumps together to form plaques, is believed to be toxic to brain cells and to prevent them from functioning properly.

Alzheimer’s Association International Conference on Alzheimer’s Disease

Biomarkers May Help Spot, Track Alzheimer’s
Results of several studies suggested the potential of biomarkers to identify and track Alzheimer’s disease. One study found that differences in levels of CD-69, a protein involved in white blood cell growth and production, distinguish between people with Alzheimer’s, people with Parkinson’s-related dementia and those who were cognitively normal. A second study confirmed previous findings: the more beta-amyloid 1-42 in the brain (as measured by PET scans), the less beta-amyloid 1-42 in cerebrospinal fluid. Another study found that individuals with mild cognitive impairment had elevated levels of beta-secretase activity in the brain compared both with healthy people and people with Alzheimer’s. A fourth study showed that the radioactive tracer compound 18F-AV-45 may have a potential role in the diagnosis and early detection of Alzheimer’s when used with PET scans.

Alzheimer’s Association International Conference on Alzheimer’s Disease

Bapineuzumab Results Are Mixed
Bapineuzumab, an experimental Alzheimer drug, was linked to brain-swelling in a study that showed no benefit of the drug for volunteers with the APOE-e4 gene. However, the treatment slowed memory loss better than existing treatments for volunteers without the gene.

Alzheimer’s Association International Conference on Alzheimer’s Disease
Family History May Add to Alzheimer’s Puzzle
A Duke University Medical Center-led study was one of only a few to examine the role of both APOE and family history combined in developing Alzheimer’s disease. In the study, people who experienced the most significant cognitive decline had a family history of the disease and one or more copies of the APOE-e4 gene. Researchers learned that APOE genotype does not tell the entire genetic story. Other genes may act independently of APOE to influence an individual’s risk for developing the disease.

Alzheimer’s Association International Conference on Alzheimer’s Disease

Experimental Alzheimer’s Drug Shows Early Promise
An experimental drug called Rember® showed promise for halting the progression of Alzheimer’s disease by breaking up tangles made of the protein tau that occur in the brain cells of those with Alzheimer’s disease. The drug improved key measures of thinking and memory in people with Alzheimer’s disease.

Alzheimer’s Association International Conference on Alzheimer’s Disease

Mild Cognitive Impairment More Common Than Expected
The rate of new cases of mild cognitive impairment in those over 70 is higher than previously expected, results from the Mayo Clinic Study of Aging show. Initially healthy participants developed mild cognitive impairment at a rate of 5.3 percent per year, two to three times higher than the rate of new cases of dementia in the same population.

Alzheimer’s Association International Conference on Alzheimer’s Disease

Drink Based on MIT Work Does Well in First Human Tests
The nutrient-rich drink Souvenaid® may offer a new option in the management of those with mild Alzheimer’s disease. The investigators found a statistically significant benefit on the delayed verbal memory task in people with mild Alzheimer’s who consumed Souvenaid. Research at MIT showed that specific combinations of certain nutrients interact to enhance synapse formation and improve cognitive function in preclinical models.

Alzheimer’s Association International Conference on Alzheimer’s Disease

Detecting Mild Cognitive Impairment and Its Transition to Alzheimer’s Disease
Scientists reported advances in understanding mild cognitive impairment (MCI) and its transition to Alzheimer’s. In one study, researchers identified abnormal structural changes in the brains of seemingly normal elderly that indicated MCI. They used a tool based on MRI images from the brains of people with Alzheimer’s disease to examine the MRI images of normal elderly and identify any remarkable structural changes. In a second study, researchers detected changes in cells that may help predict the transition from MCI to Alzheimer’s disease. Analyzing changes in levels of biomarkers in cerebrospinal fluid in people with MCI can predict the conversion to Alzheimer’s disease, especially when used in conjunction with neuroimaging and psychological tests, reported researchers.

Alzheimer’s Association International Conference on Alzheimer’s Disease

Dementia in Developing Nations May Have Been Substantially Underestimated
Researchers concluded that the standard dementia criteria might substantially underestimate the true prevalence of dementia, especially in less developed regions, because of difficulties in defining and ascertaining decline in intellectual function and its consequences. Prevalence differences between developed and developing countries might not be as large as previously thought.

Lancet online (Print: August 9, 2008;372(9637):430–432.)
Statins May Protect Against Memory Loss
People at high risk for dementia who took cholesterol-lowering statins were half as likely to develop dementia as those who did not take statins, a study showed. The study did not look at statins as a treatment for existing dementia, only as a preventive treatment. *Neurology*, July 29, 2008;71(5):344–350.

Can Midlife Use of Hormones Reduce Dementia Risk?
Women who began hormone therapy at menopause had a 24 percent reduced risk for all forms of dementia, including Alzheimer’s disease, researchers reported. Women who started hormone therapy at a later age had up to a 46 percent increased risk of dementia. *Alzheimer’s Association International Conference on Alzheimer’s Disease*

Memantine May Slow Progression of Behavioral Symptoms in Alzheimer’s
Treatment with memantine may slow the progression of behavioral symptoms, including delusions, irritability, abnormal night-time behavior, appetite and eating changes, agitation and aggression, in Alzheimer’s disease, scientists reported. It may even prevent those symptoms from emerging, they added. *Alzheimer’s Association International Conference on Alzheimer’s Disease*

Being Single in Midlife Could Raise Risk for Dementia Later
A Scandinavian study found that unmarried middle-aged people are more likely to develop cognitive impairment than their partnered counterparts. Researchers studied 1,449 Finnish people who were questioned in midlife and then again in 1998, an average of 21 years later. Almost 10 percent of those in the study were diagnosed with some form of cognitive impairment in 1998; 48 had Alzheimer’s disease. Those who lived with a partner in midlife were less likely to be cognitively impaired than all others (including those who were widowed, single, divorced or separated). After researchers took into account the effects of factors such as weight, physical activity and education, those with partners still had a 50 percent lower risk of showing signs of senility in later life than those who lived alone. Those who stayed single their entire lives had double the risk of dementia, while those who were divorced from midlife onward had triple the risk. *Alzheimer’s Association International Conference on Alzheimer’s Disease*

Ruminating Could Protect the Brain
In a longitudinal study of 9,000 subjects, the tendency to ruminate appeared to decrease one’s risk of developing dementia. Dementia was assessed at the beginning of the study and three decades later in 1,890 participants among the 2,604 survivors of the original cohort. The prevalence rates of dementia were 21 percent for those who always forget difficulties in familial settings, 18 percent for those who tend to forget, 14 percent for those who tend to ruminate over difficulties, and 14 percent for those who usually ruminate. “One possible explanation could be that some forms of rumination may be associated with effective problem-solving and are a form of cognitive activity,” said one of the authors. “Cognitive activity has been demonstrated to be associated with decreased risk for dementia.” *Alzheimer’s Association International Conference on Alzheimer’s Disease*
Baxter Alzheimer’s Drug Effective in Nine-Month Study
People with Alzheimer’s disease who were treated with Gammagard for nine months maintained cognitive function and in some cases experienced an improvement in function, according to a small study. Gammagard, an intravenous therapy of antibodies derived from human plasma, is intended to attack the disease in two ways. The antibodies target the beta-amyloid proteins thought to disrupt brain function in Alzheimer’s. Gammagard also contains anti-inflammatory properties that may activate microglial cells to help dissolve amyloid deposits, or plaques.

Alzheimer’s Association International Conference on Alzheimer’s Disease

Moms with Alzheimer’s May Pass on Risk to Kids
People whose mothers had Alzheimer’s disease may be predisposed to the disease, a study found. The link may be a dysfunction in how the brain handles sugar—something that’s probably genetic and starts years before symptoms of Alzheimer’s appear, researchers say. The researchers found that people with a mother with Alzheimer’s had a much faster reduction in the use of glucose in areas of the brain affected by the disease compared with people who had a father with Alzheimer’s or parents without the disease.

Alzheimer’s Association International Conference on Alzheimer’s Disease

Antibody Affects Beta-Amyloid Protein
Results of a Phase II study of LY2062430, an investigational anti-amyloid beta monoclonal antibody for the treatment of mild-to-moderate Alzheimer’s disease, showed that the drug bound to beta-amyloid, resulting in increased amounts of beta-amyloid in participants’ blood and cerebrospinal fluid. These results suggest LY2062430 may begin to dissolve amyloid plaques in the brains of those with Alzheimer’s disease.

Alzheimer’s Association International Conference on Alzheimer’s Disease

Elevated Calcium Levels Near Plaques Can Disrupt Neuronal Function
Using an advanced imaging technique that reveals how brain cells are functioning, researchers find that levels of intracellular calcium are significantly elevated in neurons close to plaques in the brains of mice genetically altered to develop Alzheimer’s. The study also shows how this calcium overload can interfere with the transmission of neuronal signals and activate a pathway leading to further cell damage.


August

Inhibiting Calpain Restores Synaptic Function in Mouse Model of Alzheimer’s
Researchers report that inhibiting the action of the protein calpain restored synaptic function in mice genetically altered to develop Alzheimer’s. Calpains are calcium-activated enzymes that can initiate a chain of events that result in the breakdown of proteins essential to the survival of neurons. Techniques or agents that inhibit calpain may intervene in the pathological changes that occur in Alzheimer’s disease.

Journal of Clinical Investigation, August 1, 2008;118(8)2796–2807.
11

PET Scans Help Detect Alzheimer Brain Plaques
PET scans provide physicians with a noninvasive method of detecting Alzheimer’s disease-related brain plaques, said scientists. In a small study of 10 volunteers, volunteers received injections of a marker called carbon 11 before undergoing a 90-minute PET scan. The results showed that volunteers with beta-amyloid plaques based on brain biopsies had a higher concentration of carbon 11 in certain areas of their brains than those who did not have these plaques. The study supports the use of [11C] PiB PET in the evaluation of beta-amyloid deposition in mild cognitive impairment, Alzheimer’s disease and normal-pressure hydrocephalus.

*Archives of Neurology* online (Print: October 2008;65(10):1304–1309.)

12

Physical Frailty Could Predict Alzheimer’s Disease
Physical frailty among the elderly may be linked to early Alzheimer’s disease, research revealed. The finding, based on brain autopsies of elderly individuals with Alzheimer’s, raises the notion that physical frailty in the elderly is an early symptom of Alzheimer’s—one that appears before mental decline.


28

Antipsychotic Drugs Boost Stroke Risk
All antipsychotic drugs can increase the risk of stroke, but the risk is greatest among older people with dementia, British researchers reported. The researchers believe that the risks associated with antipsychotic use in those with dementia generally outweigh the potential benefits, and, in this group, use of antipsychotic drugs should be avoided wherever possible.

*British Medical Journal* online (Print: September 13, 2008;337:616–618.)

September

8

A Blood Marker May Indicate Alzheimer’s Risk
Levels of beta-amyloid 1–42 in the blood may allow doctors to detect an individual’s predisposition to developing the disease, reported researchers. This finding has the potential to influence the way that the disease is treated. The study showed that plasma levels of beta-amyloid 1–42 increase before the onset of Alzheimer’s disease and decline shortly after the onset of Alzheimer’s. Researchers found that people with elevated levels of beta-amyloid in their blood appear to be at increased risk of developing the disease, especially if those levels begin to decrease over time.

*Proceedings of the National Academy of Sciences* online (Print: September 16, 2008;105(37):14052–14057.)

13

Brain Protein Linked to Alzheimer’s Disease
Investigators announced a link between the brain protein KIBRA and Alzheimer’s disease, a discovery that could lead to new treatments. The discovery builds upon research showing a genetic link between KIBRA and memory in healthy adults. In the study, researchers found that carriers of a certain form of the KIBRA gene had a 25 percent lower risk of developing Alzheimer’s disease.

*Neurobiology of Aging* online only
23

**Benefit of Combination Therapy for Alzheimer’s Disease**

Extended treatment with Alzheimer’s disease drugs can significantly slow the rate at which the disorder advances, and therapy with two different classes of drugs is even better at helping individuals with Alzheimer’s maintain their ability to perform daily activities, said researchers.  

26

**Active Social Life May Reduce Men’s Alzheimer Risk**

Cognitive and social activity in midlife may significantly reduce men’s risk of dementia, says a study that followed 147 male twin pairs for 28 years. Among the twins, higher cognitive activity scores predicted a 26 percent reduction in risk for developing dementia first. The study found that reduced dementia risk was most strongly associated with participation in intermediate novel activities such as home and family activities, visiting with friends and relatives, club activities (such as attending parties and playing card games), and home hobbies. Two other categories of cognitive activities—novel and passive/receptive—also reduced dementia risk but not to the same degree as intermediate novel activities. Novel activities include reading, studying for courses, and extra work (overtime or other employment), while passive/receptive activities include watching television, listening to radio, going to movies, or seeing theater, art and music shows.  
*Alzheimer’s Association International Conference on Alzheimer’s Disease*

30

**Blood Protein Tied To Alzheimer’s Disease Risk**

Low levels of cystatin C—a protein found in blood that is commonly used as a measure of kidney function—may be a risk factor for Alzheimer’s disease in elderly men. According to researchers, a 0.1-mcmol/L decrease in cystatin C between ages 70 and 77 was associated with a 29 percent higher risk of developing Alzheimer’s disease.  

October

15

**Vitamin B Supplementation Did Not Slow Cognitive Decline in Alzheimer Disease**

High-dose vitamin B supplementation in people with mild-to-moderate Alzheimer’s disease did not slow the rate of cognitive decline, according to an 18-month study of several hundred individuals.  

23

**Cystatin C Influences Beta-Amyloid Levels**

Investigators reported that in a mouse model of Alzheimer’s disease the protein cystatin C increased beta-amyloid levels by inhibiting an enzyme that breaks down beta-amyloid. Cystatin C–free mice had significantly lower levels of soluble beta-amyloid, lower levels of beta-amyloid 1–42 and fewer beta-amyloid plaques overall. Cystatin C may prove to be a new target for intervening in the beta-amyloid accumulation associated with Alzheimer’s disease.  
Scientists Identify Molecule That Helps Make Memories
Researchers identified a missing-link molecule, myosin Vb, that helps to explain the process of plasticity in the brain and could lead to targeted therapies for Alzheimer’s. The molecule moves new receptors to the synapse so that the neuron can respond more strongly to stimulation. This molecule may be part of a general delivery system in the brain and could have significance for all cell signaling.

November

1 APOE Levels in CSF Correlate with Levels of Alzheimer Proteins
A study of cognitively normal adults ages 21–88 years found that levels of APOE in cerebrospinal fluid were correlated with levels of amyloid precursor protein (APP) and tau, proteins associated with Alzheimer’s disease. The results suggest that modulation of APOE levels may increase or decrease levels of APP and tau in the brain.

3 Counseling and Social Support for Alzheimer Caregivers Reduces Depression
Symptoms of depression decreased among caregivers who received five sessions of individual and family counseling, while depression increased among those who did not receive counseling. The results provide evidence that a multi-component counseling and support program for caregivers can reduce depression.

5 Vitamin B3 Reduces Alzheimer Symptoms, Lesions
Researchers reported that nicotinamide, a form of vitamin B3, lowered levels of phosphorylated tau, a protein that leads to the development of tangles, one of two brain lesions associated with Alzheimer’s disease. The vitamin also strengthened the scaffolding along which information travels in brain cells, helping to keep neurons alive and further preventing symptoms in mice genetically altered to develop Alzheimer’s.

9 Education Blunts Effects of Alzheimer’s
Brain scans of people with the beta-amyloid plaques that are a hallmark of Alzheimer’s disease are strengthening the notion that greater education levels somehow protect against the effects of Alzheimer’s. People with more education performed better on memory and problem-solving tests than others with similar amounts of the brain plaques.
Reducing Activity of Brain Enzyme Preserves Memory in Alzheimer Mouse Model
An enzyme known to release neurotoxic fatty acids from lipids in the brain (group IVA phospholipase A2) was shown to be more active in humans with Alzheimer’s and in mice altered to develop the disease. Reducing the activity of this enzyme in mice prevented the memory problems they typically develop.
Inhibiting the enzyme with a drug also blocked neurodegeneration caused by toxic beta-amyloid proteins in cultured brain cells. Group IVA phospholipase A2 may be a useful drug target for the treatment of Alzheimer’s disease.

Nature Neuroscience online (Print: November 2008;11(11):1311–1318.)

Scientists Uncover Mechanism Linked to Neurodegeneration and Alzheimer’s
A study shed light on the formation of large rod-shaped bodies that contribute to neurodegenerative injury and dysfunction. These rod-shaped bodies, which are made up of the protein actin (necessary for cell movement and division) and its key regulatory component, coflin, appear in abundance in animal models of neurodegeneration. These bodies are especially abundant near beta-amyloid deposits and neurofibrillary tangles in Alzheimer’s disease. The study describes a key part of the process of forming actin/cofilin bodies that might be targeted in future Alzheimer therapies.


Anesthetic Isoflurane Associated with Increased Levels of Beta-Amyloid in Animal Models
Researchers reported that the commonly used anesthetic gas isoflurane was associated with increased amounts of the enzyme beta-secretase and the protein beta-amyloid in mouse models, substances that are present in elevated levels in humans with Alzheimer’s. Giving mice the drug clioquinol before administration of isoflurane decreased the aggregation of beta-amyloid. Much additional research is needed to learn whether these findings are applicable to humans receiving isoflurane. This research was funded in part by the Alzheimer’s Association.

Annals of Neurology online (Print: December 2008;64(6):618–627.)

Alzheimer’s Gene Slows Brain’s Ability to Export Toxic Protein
The APOE-e4 gene that is a risk factor for Alzheimer’s slows the brain’s ability to export the toxic protein beta-amyloid that is believed to be central to the damage caused by the disease, a study reported. The findings point to differences in the way beta-amyloid is removed from the brain depending on which APOE allele (e2, e3 or e4) is involved.

Journal of Clinical Investigation online (Print: December 1, 2008;118(12):4002–4013.)

Amyloid Deposits Found in More Than 20 Percent of Cognitively Normal Seniors
About one in five cognitively normal elderly people has signs of Alzheimer’s-related beta-amyloid plaques in the brain, which is about the same proportion as found in brains of deceased individuals who were diagnosed with Alzheimer’s disease. Researchers used PET-PIB imaging to detect areas of beta-amyloid deposits in healthy living volunteers. In the past, such plaque deposits could only be detected on autopsy. These findings have implications for preventive strategies and might lay the groundwork for predicting, before the onset of symptoms, who will develop Alzheimer’s.

Study Suggests Neuroprotective Role for Calpastatin
Scientists report that decreased levels of the protein calpastatin may play a role in Alzheimer’s disease. Calpastatin inhibits the action of another protein, calpain, which is implicated in the synaptic dysfunction and neurodegeneration of Alzheimer’s. Agents that mimic the effects of calpastatin may help prevent the neuron damage associated with Alzheimer’s.

Cholinesterase Inhibitors Reduce Behavioral Symptoms of Alzheimer’s Disease
Cholinesterase inhibitors, used to treat cognitive symptoms of Alzheimer’s disease, may also be a safe and effective alternative therapy for the behavioral and psychological symptoms of dementia, said researchers. They reviewed nine randomized, double-blind, placebo-controlled clinical trials evaluating the effectiveness of three popular cholinesterase inhibitors in managing behavioral and psychological symptoms displayed in Alzheimer’s. The trial results indicated that cholinesterase inhibitors led to a statistically significant reduction in behavioral and psychological symptoms such as aggression, wandering or paranoia when using the same dosage as administered for improving cognitive impairment.

MRI Scans Accurate in Early Diagnosis of Alzheimer’s Disease
MRI scans that detect shrinkage in specific regions of the mid-brain attacked by Alzheimer’s disease accurately diagnose the neurodegenerative disease, even before symptoms interfere with daily function, a study found. The study adds to evidence that MRI scans are a valuable diagnostic tool for Alzheimer’s disease.

A Special Type of Collagen May Help Protect the Brain from Alzheimer’s Disease
A certain type of collagen, collagen VI, protects brain cells from beta-amyloid proteins, which are believed to contribute to the development of Alzheimer’s disease, said scientists. While the functions of collagens in cartilage and muscle are well established, before this study it was unknown that collagen VI is made by neurons in the brain and has a neuroprotective role.

Enzyme Could Be a Target for New Treatments
Scientists have found that neurons die when an enzyme called HDAC1 is blocked. HDAC1 is involved in the formation of chromatin, the structural component of chromosomes. This finding suggests a role for HDAC1 as a molecular link between abnormal cell-cycle activity and DNA damage. As a result, this enzyme could be a potential target for Alzheimer’s disease therapies.
17
Study Links Beta-Amyloid Deposition to Degeneration of Neurons
To better understand the potential role of beta-amyloid in Alzheimer's disease, researchers examined whether progressive deposition of beta-amyloid in mice genetically altered to develop Alzheimer's resulted in the degeneration of neurons. Researchers focused on specific neurons called monaminergic neurons. They found that progressive deposition of beta-amyloid in the forebrains of mice resulted in extensive loss of these neurons, supporting the theory of the pathologic role of beta-amyloid in Alzheimer's disease.

21
Two Cardiovascular Proteins Tied to Severity of Alzheimer’s
Researchers found that the proteins myocardin and serum response factor lessen blood flow in the brain and reduce the rate at which the brain is able to remove the protein beta-amyloid. Beta-amyloid accumulates in damaging quantities in the brains of individuals with Alzheimer's. The two proteins could prove an effective target for future Alzheimer treatments.
Nature Cell Biology online (Print: February 2009;11(2):143–153.)

26
Brain Starvation With Age May Trigger Alzheimer's
When the brain has a deficient supply of energy due to low levels of the sugar glucose, a key brain protein, called eIF2alpha, is altered, reported scientists. This deficiency increases the production of an enzyme that, in turn, triggers production of the protein beta-amyloid that is implicated in Alzheimer's disease. This finding suggests that improving blood flow to the brain might be an effective therapeutic approach to preventing or treating Alzheimer’s, as it would improve the delivery of glucose to the brain.
Neuron, December 26, 2008;60(6):988–1009.