

Research Spotlights

Written by Jeff Worley and Alicia P. Gregory

Aging & Alzheimer's

Working to Solve the Alzheimer's Puzzle

By now, anyone who follows medical news in this country has heard the statistics. An estimated 5.1 million Americans have Alzheimer's disease. Nearly half of people age 85 and older have Alzheimer's. By 2050, the number of people age 65 and over with this disease will range from 11 million to 16 million unless science finds a way to prevent or effectively treat it. With the establishment in 1986 of the Alzheimer's Disease Research Center at UK's Sanders-

Brown Center on Aging, one of the 10 original centers in the United States, UK positioned itself as a leader in Alzheimer's research. And work has continued at a feverish pace: in 2000 to 2005 alone, 83 extramurally funded projects were under way at Sanders-Brown. The projects featured on the following pages represent only a small fraction of the total research effort in the past 25 years to understand and treat this devastating disease.



Aluminum as a Major Cause?

In the mid-'80s, William Markesbery, director of the Sanders-Brown center, chemistry professor William Ehmann, and post-doctoral fellow Mark Lovell focused on the possible role of trace metals in the etiology of the disease. Several heavy metals were thought to possibly contribute to the development of Alzheimer's, and, like any good detectives, the researchers began to investigate the list of suspects.

"We looked at aluminum first," says Markesbery, a pathologist and neurologist who has worked at UK since 1972. "The aluminum hypothesis is a reasonable one. Aluminum is the third most common element in the earth; there's aluminum dust in the air of every room in your house."

Using Alzheimer's disease brain specimens taken at autopsy, the researchers first determined bulk levels of aluminum using neutron activation analysis. Next, they utilized UK's (then) new Laser Microprobe Mass Analyzer, state-of-the-art equipment for this work, to further analyze the samples. The conclusion: there was no significant elevation of aluminum in the brain in Alzheimer's disease.

"Although there have been a few research groups through the years that have disputed this finding, other prominent and well-respected groups have agreed with us," says Markesbery.



Calcium's Role in Cell Death

In a separate but complementary project, Philip Landfield, UK professor of pharmacology, and his research group were making other discoveries about calcium's changing role in nerve cells as this relates to Alzheimer's disease. In order for nerve cells to function properly, they must maintain a narrow range of calcium concentrations. Calcium channels increase with age in neurons, flood the cell with calcium, and lead to a host of age-related, nerve cell malfunctions.

Backed by a \$1.4 million NIH award and a \$5 million award from the National Institute on Aging, Landfield's team used a powerful microscope to lower the tip of a microscopic glass tube onto the surface of a dissected nerve cell from an aged rat.

**too much calcium =
nerve cell damage**

The glass tube was attached to a sensitive electrical amplifier that measured molecular calcium channel activity. Landfield explains: "Every membrane has many different kinds of channels on it. Since we wanted to study only calcium channels, we introduced drugs known to react with and block other types of channels."

The NIH recognized the success and the potential of this work by awarding Landfield's group a \$7.5 million, five-year renewal grant, one of the largest ever awarded to UK faculty solely for research.

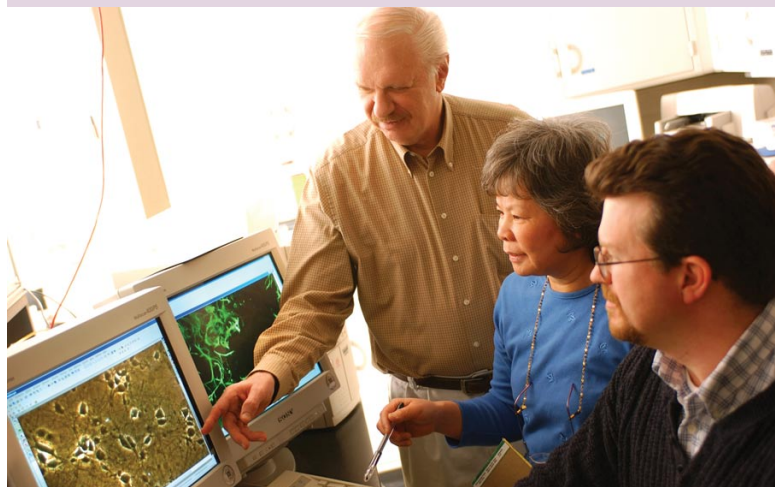
Utilizing a new technology called DNA microarray, Landfield began analyzing thousands of genes and genetic pathways to better understand how Alzheimer's progresses. His team also invented and patented technology to extract isolated nerve cells for molecular analysis. Using these approaches, the researchers were able to see which gene pathways were involved in aging and Alzheimer's disease.

"The most important thing to come out of this approach is that we identified hundreds of genes that correlated with the early phases of aging and Alzheimer's," Landfield (standing, below) says. "We were then able to assign identified genes to biological process categories to get an idea of which cellular pathways were being turned on."

Cell Pathways to the Disease

In the early- and mid-'90s, the Sanders-Brown center began working at the molecular level to try to understand the mechanisms of Alzheimer's disease. Mark Mattson, a neurobiologist, Mark Lovell, now in the UK chemistry department, and William Markesbery found that beta peptides [short molecules formed from the linking of amino acids] cause nerve cell damage by inducing a free-radical process called "lipid peroxidation" in the nerve cell membranes. Lipids are fatty or waxy substances that constitute, along with proteins and carbohydrates, the principal components of living cells.

"We found that such lipid peroxidation results in the impairment of protein function in the membrane that normally transports ions (sodium and calcium) out of the cell and glucose into the cell," says Markesbery. "This results in excessive elevation of intracellular calcium levels and reduced energy production in the neurons, rendering them vulnerable to degeneration and death."





MCI= pre-Alzheimer's

Early-Stage Alzheimer's Disease

Early detection and prevention are the keys to fighting Alzheimer's disease, according to Markesbery. And detection of the earliest phase of memory decline has become so important that there is now a term used to describe this research focus: mild cognitive impairment, or MCI.

Several UK researchers, including Stephen Scheff, a professor of anatomy and neurobiology at the Sanders-Brown Center on Aging, are working to better understand MCI. The project is focused on a group of more than 400 people who don't have Alzheimer's, but about half are at high risk of developing the disease because of their family history. All of these subjects have agreed to donate their brains for analysis after they die.

"These participants undergo extensive cognitive testing and represent a unique resource for research into the relation between neuropathologic changes and cognitive performance in aging," Scheff says. "By studying this normal group of volunteers, we're getting closer to being able to detect the earliest possible onset of the disease, and we believe that with early preventive treatment, we can slow the progression of Alzheimer's." Frederick Schmitt, a UK professor of neurology, is working with Scheff on this project.

In separate work on MCI at UK, Allan Butterfield, director of the Center of Membrane Sciences, has done a study of brain tissue of patients who had been diagnosed with MCI, finding that the brains of these patients consistently showed elevated oxidative stress. "The implications of these findings are that such stress may drive the conversion of MCI to Alzheimer's," says Butterfield, also a professor of chemistry. In this work, his lab used proteomics, the large-scale study of proteins' structures and functions, and was the first to identify which brain proteins were modified in Alzheimer's and MCI. "We found a key oxidized protein in common," Butterfield says. "This dysfunctional protein could account for the three major pathological hallmarks of Alzheimer's and MCI, which may relate to loss of memory and cognition."

With early preventive treatment, we can slow the progression of Alzheimer's.

The Nun Study

Since 1986, David Snowdon, a professor of neurology in the UK College of Medicine, has led an ongoing, well-publicized research program that is profoundly changing the way we view aging and old age. Known as the Nun Study, the project involves 678 members of the School Sisters of Notre Dame religious congregation. The sisters, who range in age from 75 to 107, have allowed unprecedented access to their personal and medical histories and undergo rigorous annual mental and physical testing.

Perhaps most remarkably, each nun also has pledged to donate her brain for Snowdon's research after she dies. During the last 15 years, 535 sisters have donated their brains, making the Nun Study a unique resource for scientific discovery.

The study has yielded groundbreaking information about what we can do to help prevent Alzheimer's disease and live active, productive lives well into old age.

The major findings from the study so far:

- If the brain remains free of strokes, dementia-like memory loss and confusion are less likely.
- Folic acid may reduce brain damage from Alzheimer's disease.
- Low linguistic ability in early life is a potent predictor of Alzheimer's disease later in life.
- Expression of positive emotions in early life such as happiness, love and hope is strongly related to longevity.