News Letter May 2009

UOG-UCSD Consortium
Institute for Micronesian Health and Aging Studies

This newsletter is our final update for research participants and their families. There are three areas of news:

1. We are closing our research project on Guam
2. We would like to summarize our research findings related to Lytico-Bodig (also known as ALS and Parkinson-Dementia complex) and late life Dementia on Guam.
3. We describe plans to store data, blood samples and tissue samples to support further research.

1. Closing the research project on Guam:
Dr. Galasko and collaborators submitted a research grant application to the National Institutes of Health (NIH) in 2007. We received news that it underwent a detailed review, and will not be funded. Dr. Galasko and the other scientists who have been involved in the research held several meetings and discussions with NIH about whether to apply again for funding. The main conclusion was that because Lytico (ALS) and Bodig (Parkinson's-Dementia complex) are now very uncommon on Guam, it will be extremely difficult to obtain funding to continue studies of aging and neurological disorders on Guam. Dr. Galasko has traveled to Guam and discussed these issues with the Community Advisory Board for the project, and also with the Project staff at University of Guam.

It is a difficult decision to close down, after the outstanding service provided by our research support staff and the strong cooperation of the Chamorro community. However, without grant funding, we will not be able to continue research on Guam.

2. Research progress and findings:
The UOG-UCSD Consortium has made a number of observations and contributions to research related to Lytico-Bodig, aging and dementia on Guam. These are outlined below.

- We continued surveillance for Lytico and Bodig and also carried out an island-wide study in 2004-2005. Since 1995, we have noted a sustained decline in both of these disorders, which are now rare on Guam. At present, Lytico is about as common on Guam as it is on the mainland USA. This is dramatically different from the period of 1944-1950, when Lytico on Guam occurred at rates of about 100 times higher than the rest of the world. The changes are best explained by an environmental factor that contributed to the high rates of ALS on Guam through the 1940s and probably the 1950s, but is now no longer present.

- We have also studied healthy aging and dementia in elderly Chamorros. Dementia means the loss of memory and other thinking abilities. Dementia occurs throughout the world, and is usually caused by problems such as Alzheimer's disease or strokes. On Guam, Bodig used to be a common cause of dementia. In 2005, we completed our survey of over 2000 elderly Chamorros throughout Guam. We found that about 12% of elderly Chamorros had dementia, which is similar to the rate reported in recent studies on the US mainland. Age is a strong risk factor for dementia: we found that the risk increased from 3% at age 65 to over 40% by age 85 or older. Dementia in elderly Chamorros usually looks like Alzheimer's disease, and strokes are the second most common cause. Bodig affected less than 1% of Chamorros aged 65 or older.
Although there is no treatment that slows down Alzheimer’s disease, new research approaches are being studied all over the world. The risk of strokes can be lowered by treating high blood pressure, diabetes and heart disease, and using antiplatelet medications as prescribed by a physician. Our studies suggest that Chamorros in their middle years should be examined and treated for risk factors such as high blood pressure, high cholesterol, obesity and diabetes, to help maintain good brain function in aging.

- We have examined whether genetic (inherited) risk contributes to Lytico, Bodig and dementia in Chamorros by studying DNA from blood samples. Dr. Jerry Schellenberg, who recently moved from the University of Washington to the University of Pennsylvania, found that changes in a gene called TAU influenced the risk of all three of these diseases. People with certain types of TAU genes had a 2-3 times higher risk of developing Lytico, Bodig or dementia. This accounts for only a small part of the overall risk. In recent studies, Dr. Schellenberg’s group found evidence that there are other genes that may add to the risk, and have been working on trying to identify these genes. We think that genes by themselves do not cause Lytico-Bodig, but interact with aging and environmental factors to result in the disease.

- It is difficult to study the environment, especially when so many things on Guam have changed since the 1940s. Based on questionnaires from subjects about their lifestyle, diet and habits when growing up on Guam, we found that preparing or eating fadang as a young adult led to a slightly higher risk of developing Bodig or late-life Dementia. The risk for Bodig was higher among men than women. This does not prove that fadang caused Lytico-Bodig. It is possible that some other part of lifestyle or exposure that was more common in people who ate fadang is the true risk factor. Feeding fadang to animals does not produce changes in their brains that look like Lytico-Bodig. In recent work, scientists in Maryland and Vancouver found that rats fed with a fadang extract walked more slowly, and showed damage in areas of the brain involved in Parkinson's disease in humans. We are continuing to collaborate with scientists who work on fadang as a toxin, but the case is certainly not conclusive.

Dr Paul Cox suggested that fruit bats (fanihi) ate cycads and humans who ate fruit bats could have accidentally eaten cycad toxins, including one called BMAA. We tried to detect BMAA in brain tissue in Lytico-Bodig and were unable to find it there. We also found that people who had developed Bodig whose relatives we interviewed did not have a history of eating fanihi more often than elderly Chamorros who do not have brain problems. Therefore we do not support this theory.

Because of previous research on the mineral content of the water on Guam, we collaborated with scientists from the US Geological Survey, who extensively sampled and examined water and rocks from all over Guam. Their measurements did not detect an unusual pattern when they compared findings to those from areas in the Western USA.

- Many of our research participants will recall having brain MRI scans. Dr. Jeffrey Kaye (from Oregon Health and Sciences University) measured the sizes of different parts of the brain, using these MRI images. He detected loss of brain tissue in patients with Bodig or with dementia compared to healthy elderly Chamorros. The damage greatly affected the hippocampus, an area of the brain important in forming new memories. These findings are the same as those in studies of dementia on the US mainland. It is possible that in the future, measurement of brain structures by MRI will be routinely used in the diagnosis of dementia.

- Over the years, we have developed a bank of brain tissue obtained at autopsy. We have studied the tau protein that builds up in the brain in Lytico-Bodig, and more recently studied a
novel protein called TDP43, which was identified in ALS (Lytic) in patients in the USA. Nerve
cells in areas of the brain affected by Lytic and Bodig contained abnormal clumps of TDP43.
We do not yet know why tau, TDP43, and other proteins form clumps in nerve cells. However,
similar clumping of a variety of proteins occurs in disorders such as Alzheimer’s disease and
Parkinson’s disease. Researchers throughout the world are trying to understand these
processes better, and hope to develop new forms of treatment to modify or reverse these
changes.

3. Plans to store, bank and share research data and samples.

We are using the small amount of remaining funds to make preparations to store the data and
samples that we have collected over the years. This will allow us to carry out future research
and to share these with other researchers. This could be useful if new research techniques
become available. During 2008-2009, we have been preparing lists of the data, DNA, blood
samples, brain tissue and MRIs that were collected, and are setting up a system of storage. We
aim to allow access to these materials from interested researchers throughout the world. Dr.
Schellenberg and colleagues are interested in applying for new grant funding, with a focus on
DNA research. We are only able to maintain staffing of the research offices at UOG through
June 2009. Unfortunately, we are no longer able to visit all of our research participants at their
homes, as we have done in the past.

Records of subject evaluations that were carried out by the extramural NINCDS Field Station on
Guam (1959-1982) will be archived at the Library of the University of Guam. Research
publications related to our research will be kept at MARC (Micronesian Area Research Center),
also at the University of Guam.

Dr. Douglas Galasko at the University of California in San Diego (UCSD) has established and
will maintain a comprehensive electronic database which contains all clinical information
collected during our studies. Blood samples collected in the past 10 years are stored at UCSD.
DNA samples will be stored by Dr Jerry Schellenberg at University of Pennsylvania. Brain tissue
collected at autopsy will be stored by Daniel Perl at Mount Sinai Medical Center, New York.
Electronic files of MRI images will be stored by Dr Jeffrey Kaye at Oregon Health and Sciences
University. All data kept at sites other than UCSD are kept only by study identification number
and are not linked to any names or other personal information.

Dr. Galasko will make these resources known to researchers by describing them on the UCSD
website and on the AlzForum website, which will list contact information for him and the other
scientists who are helping to store data and tissue. If we share data with other investigators, it
will be done in a way that does not allow specific research participants to be identified. As part
of developing these plans, we have had discussions and taken advice from the National Institute
of Aging and our Community Advisory Board on Guam.

4. The latest news on Alzheimer’s disease, Parkinson’s disease and healthy brain aging:

New research was presented at the International Conference on Alzheimer’s disease in
Chicago, July 2008. The current standard of treatment for Alzheimer’s disease is Aricept and
two other drugs (Exelon and Razadyne) that act through the same mechanisms. These also
have effects in other dementias. New treatments are needed, particularly to try to slow the
progression of Alzheimer’s disease. Many drugs are being tested, and results of studies were
presented at the Conference. Unfortunately the results of studies of statins (cholesterol lowering
drugs) and a drug called Flurizan were negative. Positive early stage studies were presented for
a drug called Dimebon, which improved memory abilities in patients with Alzheimer’s disease, and for Rember, which appeared to slow progression of the disease over 12 months. Both of these drugs are now undergoing larger studies to see whether these results can be confirmed.

Research continues to support the belief that exercise can benefit the brain. In one study, elderly people who were previously inactive started a program of either regular exercise or stretching and yoga. Those who exercised showed improvement in blood pressure and insulin levels, and also performed better on tests of memory, learning and concentration compared to the stretching and yoga group. Other studies found that older people who exercised regularly had a lower risk of developing Alzheimer’s disease or strokes than those who did not. Some types of diet can affect the brain. Eating fish (not fried) (rich in Omega 3 fatty acids) 1-2 times per week, or eating a ‘Mediterranean’ type diet, may also decrease the risk of Alzheimer’s disease.

In Parkinson’s disease, a number of new genes that modify risk have been discovered. These appear to influence not only rare cases of strongly inherited Parkinson’s disease that runs through a family, but also affects people with onset later in life who may lack a family history. Based on genes discovered to date, between 10 and 25% of people with Parkinson’s Disease may have a genetic component that contributes to their risk.

5. In conclusion:
We would like to thank the many people who participated in our research studies over the years. We deeply appreciate your warmth and generosity in allowing us to conduct testing, collect data and obtain blood samples and MRI scans from you. We have fond memories of the many home visits that we conducted, where we were always impressed by the warmth, hospitality and strong family support that are such a key part of the Chamorro culture. We appreciate your outstanding support and efforts as research participants and will always cherish wonderful memories of our research experiences on Guam.

Douglas Galasko, MD
Professor, Department of Neurosciences, UCSD

Ulla-Katrina Craig, DrPh,
Professor, University of Guam

Investigators of the UCSD-UOG Lytico-Bodig Research Consortium

Staff of the Micronesian Health and Aging Study,
University of Guam