



V A B I O R E P O S I T O R Y B R A I N B A N K N E W S

A YEAR IN REVIEW

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SPECIAL POINTS OF INTEREST:

- The work of the VABBB has been published in an ALS scientific journal, and noted in several news sites
- An ALS caregiver describes her experiences supporting her father
- Tissues from the VABBB have already been used in various research studies

VABBB IN THE NEWS

The VABBB published a paper in the December 2013 issue of the scientific journal, *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*

We recently published a paper describing the methods and current status (as of 12/12/2012) of the VABBB. The paper noted that Veterans with

ALS are eager to help ALS research as noted by the 56% success rate in enrolling those Veterans we contacted; this rate is very high. Also, we were happy to report that the VABBB has successfully conducted tissue recoveries in 100% of cases where we were notified and the family wanted to proceed with the donation. This success is due to the extraordinary dedication of the Veterans and their families in making this donation upon the Veteran's death, and the medical professionals and numerous others who assist the VABBB in performing these tissue donations in 37 states so far.

Another notable finding is that our sample of Veterans has a longer average survival than reported in previously published studies. For example, those Veterans who had died



The Boston VABBB team: (from left) neuropathologist Dr. Thor Stein; project coordinator Latease Guilderson; data manager Sally Perkins; program support assistant Melissa Weiner; principal investigator Dr. Neil Kowall; project coordinator Shelley Amberg; and director of scientific operations Dr. Christopher "Kit" Brady. (Photo by Frank Curran)

had an average survival (from initial ALS symptom onset) of 8 years, whereas those still alive as of 12/12/12 had an average disease duration of 14 years. This is much longer than the often-cited survival of 3-5 years in ALS. The reasons for this relatively longer survival are unknown; however, the VABBB is collaborating with

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HIGHLIGHTS

- 56% of Veterans contacted by the VABBB agreed to enroll
- 240 Veterans from 47 states have enrolled, with tissue recoveries conducted on 100 Veterans in 37 states
- Veterans with ALS in the VABBB appear to have a longer survival on average than previously published studies

VABBB COLLABORATES WITH NATIONAL DISEASE RESEARCH INTERCHANGE (NDRI)

The VABBB recently began working with NDRI in order to streamline the tissue recovery process

In the fall of 2013, the VABBB began a partnership with the National Disease Research Interchange (NDRI), a leading human tissue resource center, to assist in our tissue



recoveries. NDRI has been dedicated, for more than 33 years, to the procurement and distribution of human tissues for biomedical research and has procured more than 300,000

organs and tissues that have been used in thousands of research studies. Partnering with NDRI has allowed the VABBB to streamline the tissue recovery process, which involves coordinating with pathologists, hospitals, and funeral homes across the United States. Through our relationship with NDRI, we have

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THE EFFECTS OF ALS ON THE MIND

Research on the effects of ALS on the mind may help scientists better understand how ALS impacts the nervous system

- ◆ It has been well known for over 140 years that ALS affects the ability to move, swallow, and breathe.
- ◆ More recently, attention has turned to better understanding the effects of ALS on thinking and behavior.
- ◆ New insights into the effects of ALS on mental abilities suggest that clinicians should be assessing thinking and behavior in addition to their regular assessments conducted at clinic visits.

Changes in mental abilities were only sporadically noted in the research literature on ALS until the late 1990s. Since then, the effects of ALS on thinking and behavior have received heightened attention by ALS clinicians and researchers. The National Institutes of Health, American Academy of Neurology, ALS Association, and numerous other American and international organizations now recognize that changes in thinking and behavior should be considered when assessing persons with

ALS (PALS) and in research into ALS.

Changes in mental abilities may or may not occur in PALS. For example, one PALS may have difficulty moving his/her arms and legs but can think quite clearly, whereas another may have less difficulty with movement but more difficulty remembering things or being more apathetic. These differences in symptoms may be related to one's environment and/or genetics that can vary across individuals. Therefore, current and future research on ALS must focus not



Photo credit: NCI/Rhoda Baer
only on movement, but on the mind as well.

Those of you in our study are aware that over the years we have asked questions about how ALS affects movement, eating, drinking and breathing. Because of the importance of understanding changes in thinking and behavior in ALS, as briefly described above, the

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CAREGIVER CORNER

BY KRIS JURKA, ALS CAREGIVER

During each installment of caregiver corner, a family member of one of our participants, will describe his or her experiences caring for a loved one with ALS

Gardening, cooking, and bowling were lifelong passions for my father, Henry Mikolajczyk. He had participated in the United States



Henry (left) and his bowling friends
Photo courtesy of Kris Jurka

Bowling Congress for almost 50 years when he was diagnosed with ALS in November of 2012. Perhaps it was a

blessing that he bowled, for he sought medical help because he could no longer hold a 16-pound ball.

That December, Dad and I went to see a neurologist at the University of Chicago. A battery of tests, including an electromyogram (EMG), confirmed the diagnosis of ALS. I didn't know what ALS was at first. I remembered the baseball player Lou Gehrig and his speech at Yankee Stadium the day he retired from baseball due to this disease. I truly did not comprehend what it meant to lose voluntary control over one's muscles, hands, legs, swallowing and breathing, and eventually become paralyzed with one's mind intact, until I watched it happen to dad. There is neither a cure nor effective treatment for ALS.

When my parents moved from their home to mine on January 1st, dad could still get dressed and hold a cup of coffee. By April, my sons, two wonderful part-time aides, and I were helping him with everything that required his hands: from wiping his nose, to changing TV channels, to brushing his teeth. ALS became more intrusive in our lives, and we battled to preserve dad's independence and dignity. He always talked about the hopes of a cure and the importance of research.

Dad was admitted to the ER with pneumonia in October. His battle with ALS ended in October of 2013, only 10 months after his diagnosis.

Dad's final wishes were to donate his brain for research to help find a cure, and

"Dad's final wishes were to donate his brain for research to help find a cure, and I was willing to do whatever necessary to make that happen."



Kris and her father, Henry
Photo courtesy of Kris Jurka

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CAREGIVER CORNER CONT. FROM PAGE 2

I was willing to do whatever necessary to make that happen. I didn't know that it isn't a simple task. I also did not realize that tissue donation is usually something that has to be set up prior to an individual's demise. Dad passed away on a Saturday. On Sunday evening I found the ALSA site that lists several options for donating tissue. The local research center that I called first told me that in order to donate tissue, dad had needed to complete the paperwork in advance and/or be a

patient there. Though it was wonderful that that the donation organizations were able to promptly answer my late-night calls, I ran into the same barrier with each call I made.

After several hours, I called a VA hospital in Boston. I am so thankful that Sally Perkins and Latease Guilderson were able to help me. I had to read, complete, and return the 12 page consent form, which I received by fax while I was at the funeral home. The Boston VA group coordinated everything. There was nothing needed from me

nor any costs to our family to do this, even though we were states away. I was also told that if we were to have an open casket, there would not be an issue. It was my dad's final wish to help with research. On the day we put my father in his final resting place, we attended the MDA "A Night of Hope" in Atlanta, Georgia, an evening championing ALS research.

Please consider the gift of tissue donation for research. I'm sure the thought of our family and friends being touched by ALS in the future was on my father's

mind. His was the ultimate gift in furthering ALS research, and I am humbled. I have been blessed to have such a kind and loving father in my life, but more blessed that I was able to give back to him by being his caregiver.

HAVE A STORY TO TELL?

Thank you to Kris Jurka for her thoughtful insights into being an ALS caregiver.

If you would like to contribute to the next installment of Caregiver Corner, please contact us at **866-460-1158**

VABBB IN THE NEWS CONT. FROM PAGE 1

Health Science Specialists, Sean Walker (left) and Jim Averill, members of the Tucson VABBB team, handle central nervous system tissue (Photo by Nicole Thurston)

other ALS researchers to examine whether there are genetic or environmental reasons that may explain these findings.

We also found that 97% of cases had ALS confirmed during the neuropathological diagnosis process, which is a very high rate of confirmation of the diagnoses made by the Veterans' neurologists. Also, the average age of initial onset of ALS symptoms in the currently living sample was 53, whereas

it was about 59 for those who had died. The average age of the currently living sample was 68, as was the average age at death for those who had died. Finally, we reported that although the logistical details of conducting tissue recoveries nationwide are complicated, the VABBB has been established as a brain bank with a substantial supply of research-grade tissue and

health information that is readily accessible to ALS researchers. Please see the article, "New Research Projects using the VABBB" (p.4) in this newsletter, which describes some of these current studies.

CITATION:

The Department of Veterans Affairs Biorepository Brain Bank: A national resource for amyotrophic lateral sclerosis research. Christopher B. Brady, Katrina T. Trevor, Thor D. Stein, Eva Y. Deykin, Sally D. Perkins, James G. Averill, Latease Guilderson, Ann C. Mckee, Stephen W. Renner, Neil W. Kowall. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration Dec 2013, Vol. 14, No. 7-8: 591-597.

VABBB: List of Publications and Websites

Stories about the VABBB have appeared in several venues this year including:

- ◆ VA Research Currents
- ◆ Veterans Healthy Living Magazine
- ◆ ALS Association
- ◆ Muscular Dystrophy Association, ALS Division (MDA/ALS)
- ◆ Prize4Life
- ◆ Facebook

For links to these articles, check out the "VABBB In the News" section on the VABBB website.

http://www.research.va.gov/programs/tissue_banking/als/VABBB-in-the-news.pdf

We would be happy to answer any questions and provide additional information about these stories.



Photo credit: CDC/Amanda Mills

Make sure to visit the "VABBB In the News" section on our website for the latest stories about the VABBB

NEW RESEARCH PROJECTS USING THE VABBB

The purpose of the VABBB is to support ALS research. Since the last issue of our newsletter, we have more than doubled the number of new projects approved to use samples and information. As can be seen in the summaries below, researchers have been studying both brain and spinal cord tissue donated by Veterans to the VABBB.

Studies in Progress

Understanding Defects in Vulnerable Brain Motor Cortex Neurons

The death of motor neurons is a major effect of ALS and involves the progressive dying of motor neurons found in both the spinal cord and a region of the brain involved in the voluntary control of movement, the motor cortex. The focus of this study is to better understand what makes motor cortex neurons vulnerable to degeneration. The researchers have already identified several ALS disease pathways using a mouse model of ALS, and would now like to see if findings in the mouse model can be reproduced in motor cortex neurons in brain tissue from patients with ALS. This research will help determine which disease pathways are most important in ALS and provide for the development of long-term treatment strategies.

Genetic Studies of Familial and Sporadic ALS

Genetic discoveries are revolutionizing how we think about ALS and other neurodegenerative diseases. Genetic causations for two thirds of familial ALS cases and for approximately 10% of the more common sporadic form of the disease have been recently discovered. To further identify the genetic factors underlying familial and sporadic forms of ALS, researchers are looking at the genes from large numbers of ALS patients from around the world, including our Veteran population in the VABBB. The technologies for this genetic research include methods to look at gene differences (polymorphisms) between individuals and direct sequencing of all genes within the human genome. With the accelerated pace of gene discovery in ALS, many more causative genes will undoubtedly be identified in the near future. Importantly, these findings may result in earlier diagnosis, improved clinical care and the development of earlier treatment strategies for patients with ALS.

NDRI COLLABORATION

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been able to increase our tissue recovery network and to strengthen our ability to conduct tissue donations throughout the US. **This new collaboration does not result in our families having to do anything new when the time comes for tissue donation.** Families will still call VABBB

staff as before to notify us of the impending passing of the Veteran, or just after his or her passing. Upon being notified, VABBB staff works with NDRI staff to coordinate the tissue recovery. We strongly believe that this relationship will allow us to maintain our tradition of

obtaining tissue donations in the most respectful, ethical, and expeditious manner without compromising the quality of our Veterans' donated tissue specimen. We look forward to continuing our work with NDRI in order to help carry out the wishes of Veterans and their families in an

effort to support ALS research.

ASK THE DOCTOR:

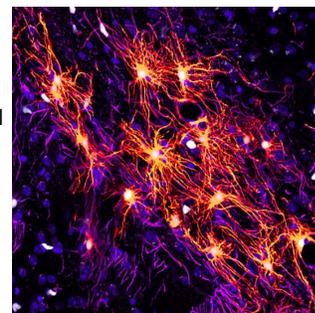
Do you have a question about ALS? Please give us a call at 866-460-1158, and we may use it in an "Ask the Doctor" segment in our next issue.

Promoting the Protection of Motor Neurons in ALS

The mechanisms responsible for the unusual sensitivity of motor neurons to cell death in ALS are unclear. The focus of this research is to identify the processes that affect motor neuron health and, importantly, attempt to regulate these factors to promote neuronal protection. Specific cell death pathways are to be studied in a mouse model of ALS and then in human ALS tissue provided by the VABBB. The ultimate goal is to identify potential therapeutic targets that could be used to reduce motor neuron degeneration. This would help develop treatments that may preserve neuromuscular function in ALS patients.

Role of Cell-Cell Communication in ALS

Cells often "talk" with each other through cell surface regions known as gap junctions. Cell-cell communication occurs through the exchange of molecules in these regions. This research aims to better understand how nerve support cells (astrocytes) communicate with motor neuron cells through gap junctions and, thereby, influence motor neuron health. The research results will contribute to further understanding the participation of crucial support cells in ALS and how these cells may promote motor neuron death. Human ALS tissue from the VABBB will be used to test whether previous findings in mouse ALS models are reflected in the human disease. This work is an important step towards designing therapies for ALS.



Nerve support cells (astrocytes) "talk" with each other through gap junctions. Photo credit: Dr. Takashihiro Takano, University of Rochester

Completed studies

Researchers showed that cells that normally support motor neurons in the spinal cord may instead make the disease worse. The researchers examined spinal cord cells called oligodendrocytes, which provide support to motor neurons. Poorly functioning oligodendrocytes were prevalent in an animal model of ALS, and were also found in human ALS tissue that was provided by the VABBB. These findings reinforce that ALS progression may affect other types of cells besides motor neurons. Therapeutic approaches to improve oligodendrocyte function may be helpful in preventing motor neuron death in ALS. This study was published in the journal *Nature Neuroscience* in March, 2013.

RECENT ADVANCES IN ALS THERAPY

The following is a review of various drugs and therapies being tested for ALS

Numerous therapies are presently being tested for ALS. Most are drug clinical trials; however, other therapies using stem cells, medical devices, and exercise are also being evaluated. In this brief review, we discuss current (as of December, 2013) findings about some of the new drugs being tested for ALS and some other therapies.

Riluzole, approved to treat ALS in the mid-1990s, remains the only approved medication. Unfortunately, a number of subsequent clinical trials have failed to discover new drug therapies for ALS. Recently, a large trial of **Dexpramipexole**, which initial studies suggested would be effective, concluded that the drug was not effective. Other recent trials of **lithium**, **ceftriaxone**, and **olesoxime** also found

these drugs to be ineffective in treating ALS.

Many new drug therapies continue to be evaluated, however. **Arimocloamol**, an oral compound that induces protective protein production mechanisms, is now being tested in patients with familial ALS, but no results are available yet.

Tirasemtiv, an experimental drug that increases muscle power, is now being tested in ALS. It does not slow down the progression of ALS but may help preserve muscle strength.

Masitinib, **Fingolimod**, and **Tocilizumab** are immune system modulators now being tested in clinical trials.

Ozanezumab, a drug that protects the neuromuscular junction, and **Rasagiline**, a drug approved to treat Parkinson's disease are also being tested in ALS patients.

Pyrimethamine, a drug that reduces a protein that is abnormal in some people with familial ALS called SOD1, is also in clinical trials.

Recent animal studies (2013) show that targeting RNA with antisense oligonucleotides (ASO) to reduce the production of an abnormal form of the protein C9orf72, the commonest genetic cause of ALS, is well tolerated and effective. Hopefully this will lead to an ALS clinical trial in the near future.

Other therapies are also being evaluated. For example, initial studies on the safety and efficacy of using stem cells to repair the neuron damage caused by ALS are being conducted in the U.S. and other countries. Other studies are examining medical devices, such as those that can prolong respiratory function by conditioning the diaphragm, and are



Photo credit: CDC/Amanda Mills

testing other therapies, such as whether exercise can prolong muscle function in ALS. Furthermore, a number of drugs are currently being tested to treat symptoms related to ALS, such as excessive saliva production and muscle cramps.

Given the large number of drugs and other therapies now being tested there is reason to be hopeful that improved treatments will be approved and available for ALS patients in the next few years.

For up-to-date information about ALS treatment please visit these websites:

<http://www.ninds.nih.gov/disorders/amyotrophiclateralsclerosis/ALS.htm>

<http://www.alsconsortium.org/trials.php>

<http://www.alsa.org/research/about-als-research/>

EFFECTS OF ALS CONT. FROM PAGE 2

VABBB has decided to start giving a brief survey about thinking and behavior to those enrolled in our study. The information that we collect about thinking and behavior will add value to the information that we already collect about the physical aspects of ALS, and also make the tissue donations even more valuable to ALS researchers.

Taking the new survey about thinking and behavior is completely voluntary and declining to participate has no effect on either your continued partici-

pation in the VABBB or VA benefits to which you and your family are entitled. Because we know that answering additional questions during our regular call may be time consuming and difficult to do, we plan to mail the survey to be completed by a family member who knows our Veteran PALS well. We feel that having a family member complete the survey would place the least burden on those who have difficulties with speaking and/or writing. As many of you know, we already speak with your family

members over the telephone to see how our Veterans are doing in cases where using the telephone is difficult. This new assessment being done by mail (or in some cases over the phone if it is more convenient to do so) is an extension of that idea.

We will ask for your permission to begin these assessments during a future telephone call. You may choose whether or not to give your permission for us to ask your family member these questions about thinking and behavior.

You may also change your mind in the future and decide to have us stop asking these questions. As with all of the information collected about you during your participation in the VABBB, the results of this survey are kept strictly confidential. We would be happy to answer any questions and provide additional information about this topic.



Photo credit: NCI/Rhoda Baer

GULF WAR VETERANS' ILLNESSES BIOREPOSITORY BRAIN BANK SEEKS VETERANS OF THE 1990-1991 GULF WAR ERA

The Gulf War Veterans' Illnesses Biorepository (GWVIB) brain bank is seeking Veterans of the 1990-1991 Gulf War who would like to participate in research about conditions affecting Gulf War Veterans. Veterans enrolled in the GWVIB complete surveys about their health every six months or so, and upon their death, donate their brain and other body tissue for future Gulf War Veterans' Illnesses research.

Veterans can begin helping now by enrolling today, even though the tissue donation may occur many years from now. This will allow researchers to

learn as much as possible about the health of an enrolled Veteran and how it may change over the years.



Newly arrived troops march to a processing area after disembarking from an aircraft during Operation Desert Shield (By Staff Sgt. F. Lee Corkran)

All Veterans of the 1990-1991 Gulf War era living in the United States, regardless of whether they served in the Gulf region or are experiencing symptoms are eligible to participate in the GWVIB brain bank. Your

decision to donate can be changed at any time.

This is the first time that any study has tried to start a national biorepository for Gulf War Veterans. The study will find out how to best set up a Gulf War Veterans brain bank and to see if there are enough Veterans who will volunteer to participate.

Additional information about this study can be found at (http://www.research.va.gov/programs/tissue_banking/gwvib/) or by calling toll-free **855-561-7827**.



GWVIB coordinator, Shelley Amberg, explains study to potential participant (Photo by Frank Curran)

DEPARTMENT OF VETERANS AFFAIRS BIOREPOSITORY BRAIN BANK

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The views expressed in this newsletter are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs

Co-enrollment for current VABBB ALS Study Participants

Participants in the ALS Brain Bank who are also Gulf War Veterans may be eligible to co-enroll in the Gulf War Veterans' Illnesses Biorepository Brain Bank. If you are interested, please call us at **855-561-7827**

THANK YOU

Department of Veterans Affairs Biorepository Brain Bank



We are deeply grateful to all the Veterans who have decided to make this generous after-death organ donation supporting the VA's commitment to ALS research.

While no one can say when ongoing scientific investigations will discover the magical key that unlocks the secret of this destructive disease, it is certain that without the very precious gift of neurologic tissues, progress would be much slower. We are also deeply grateful to Veterans' families and caretakers who have done everything in their power to fulfill the Veterans' wishes of organ donation.



May is National ALS Awareness Month!

We're on the Web!
http://www.research.va.gov/programs/tissue_banking/als/