



Volume 19, Number 2



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New York
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Spring 2008, Volume 20, Number 3

The Eleanor & Lou Gehrig MDA/ALS Research Center at Columbia University

This issue of the Eleanor and Lou Gehrig MDA/ALS Newsletter is dedicated to the courage and strength demonstrated by:

Barbara Bluespruce, Sophie Brown, Howard Bryan, Deborah Berniker, Robert Cooke, Lawrence Contillo, Herbert Carter, John DeGaetano, Renee Foley, Frank Guisto, Virginia Ianari, Roberta Martin, Jennifer Marcy, Lillian Michaelson, Neil Potter, Beverly Ryan, Leonard Shore, Henry Sienkiewicz, Stanfred Silver, Bruce Sinder

From the desk of Hiroshi Mitsumoto, MD

Dear Friends,

We just returned from the 60th annual meeting of the American Academy of Neurology, which took place on the week of April 14th in Chicago. During this 3-day scientific meeting, there were several sessions dedicated to ALS. The highlight was Dr. Petra Kaufmann's report on the results of the CoQ10 clinical trial. In this newsletter, she has a special report, so I will not elaborate. Although I am part of the study and thus any praise I make may be considered self-serving, I cannot help but point out that this study had almost no missing data, which is truly remarkable. Many clinical trials are marred by missing data which appears to be an almost inherent problem. I have to congratulate all the investigators. I would say this study was the result of an incredibly strong collaboration between our clinical unit and the Biostatistics Department at the Mailman School of Public Health. The study result was disappointing but showed a non-refutable result. One audience member at the meeting commented that it was a pity to have taken such a long time (3 years) to complete the study and find this negative result. Dr. Kaufmann answered that the CoQ10 study had a dual objective during the 3-year study period: the first was to determine the best dose from two doses, and the second was to find if the best dose selected showed any evidence for futility. If this were a conventional study, that is to study the efficacy of the drug, it would take a longer time period and require 800 patients. It was a big savings for the number of the patients required to complete the study.

Another fascinating discovery

discussed at this meeting was a protein called TDP-43, which was discovered only a couple years ago. TDP-43 is a nuclear ribonucleic protein family which is known to control RNA expression in the cells. In ALS and related conditions, this protein is abnormally accumulated, forming an inclusion body inside motor neurons and other cells such as glial cells (supporting motor neurons). Inclusion body is an abnormal cell constituent which should not be present in normal cells. You may have heard that ALS and other neurodegenerative diseases such as Alzheimer's disease or Parkinson's disease are termed as proteinopathy (meaning disease of protein dysfunction). Proteinopathy is characterized by abnormal protein accumulation or aggregates, most likely abnormal in amount and abnormal in quality. Somehow manufactured proteins are abnormal in structure and thus protein moiety becomes abnormally sticky, promoting aggregation of dysfunctional protein molecules.

Now, a number of mutations of the gene responsible for TDP-43 protein have been reported as the cause of familial ALS. It is most intriguing that the TDP-43 aggregates are found in many different forms of ALS, including sporadic ALS (which is the most common form of ALS), ALS associated with frontotemporal dementia, frontotemporal dementia without ALS, Guamanian ALS, ALS in Kii Peninsula, and other familial ALS except of SOD1 mutation. It is mind boggling to find that these TDP-43 aggregates are not found in the SOD1 mutations of either patients or mice carrying SOD1 mutation. (continued on page 2)





The Eleanor and Lou Gehrig MDA/ALS Research Center



From the Director's Desk

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THE ALS CENTER GETS A MAKEOVER

Thanks to the money raised at the Spina Golf Outing that was held last June in memory of Carol Spina, the ALS Center is getting a makeover! There will be new carpeting and chairs in the waiting room to make it more comfortable for patients and their families. The reception desk will be redesigned for wheelchair accessibility. New center signage, with updated faculty and staff information, will make it easier for patients to navigate through the ALS Center.

Waiting for the elevator will also become less of a burden. There will be sitting and informational areas near the elevators. We couldn't have started these renovations

without the Spina family's generous support! *THANK YOU!*

SOD1 mutations are the most common types of familial ALS, and the animal model called 'ALS mice' are all based on transgenic models of this SOD1 mutation. We ask why most ALS has TDP-43 accumulation, but not in the SOD1 mutation. The investigators have been using this SOD1 mutant animal model for the past 12 years, and the majority of basic research papers are derived from studies in SOD1 mice. We start raising the question of whether the investigators have been using the wrong model for most ALS types. It obviously generates a serious concern. It is urgent that we resolve whether the question I raised is valid or whether there is something more to it. Although SOD1 transgenic mice are the best model for ALS to date, we realize that we need to be more cautious about the results coming from therapeutic trials studied in these animal models. We desperately need another and better model than SOD1 transgenic models, and I hope investigators are already working to generate TDP-43 transgenic models.

If we can study the cause and cure of ALS in mice and cell models, we will find the solution relatively easily. It is true that mice and humans are very different, and furthermore, it is uncertain if the model one has studied is the right one. You can imagine more primitive animals and cell models may have more limitations in extrapolating their results into humans. We have to study simple, cost-effective models, but we may need to come back to the patients with ALS for appropriate investigations. Yet, it is very true that studying human patients poses many insurmountable limitations. Personally, I propose we need to study patients as much as we can in many different settings. Clinical trials are the best example.

There are very interesting models that were presented at this annual meeting. There was a report studying a fruit fly with SOD mutations. In fact, there is a zebra fish model and a worm model called *C. elegans*, all of which carry SOD1 mutations. These models are very useful in studying biological and molecular mechanisms, but I have to express my honest feeling that they would not represent a human disease.

At this meeting, there were investigators who have been involved with an NIH-funded multicenter nutritional/respiratory study. The last patient will be

completed in June and the data will be analyzed. This is one of the many studies we have been participating in. We will have a slew of new results that will be reported in the next year or two. We very much appreciate the patients and families who participated in the study.

Finally, I would like to bring you up to date. Our Center continues to be very busy as usual. The genetic-environmental epidemiology study is in the final stretch and recently we started a prospective oxidative stress study in patients with ALS. Mary Kilty, a coordinator for both studies will give us an update in the next newsletter. We have just enrolled the first patient for pseudobulbar affect (abrupt forced laughter or crying spells in patients with bulbar ALS) and are almost ready to start a new clinical trial with a Knopp neuroprotective drug. Dr. Jinsy Andrews started a small safety study with lithium. You can find her brief study description in this newsletter. Dr. Arbesman, a dermatologist, and Columbia dermatology colleagues are now testing the feasibility of skin as a marker for ALS. This is very innovative and we are all excited about this study. Dr. Arbesman has a section describing his project. Working with the Harvard and Columbia stem cell investigators, we performed skin biopsies from patients with sporadic and familial ALS. We are expecting to hear some exciting news from them. Dr. Amy Chen wrote a brief follow-up note in this newsletter updating oxidative stress and exercise study in patients with ALS. Drs. Basner and Atkeson, Columbia pulmonary specialists, are working with the non-invasive ventilator as to how to improve the effectiveness of this assistive device with intensive monitoring and detailed instruction. Gabriela Harrington, ALS nurse specialist, is working with Dr. Rabkin to improve satisfaction and time-effective allocation of the multidisciplinary team at our ALS Center. Dr. Kaufmann and Kate Bednarz are working to obtain NIH approval for the second phase data entry for DNA banking.

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Meetings like the American Academy of Neurology are an important opportunity for us to exchange ideas and to see what's happening at other major centers. Many other ALS Centers are busy as well doing a number of the same collaborative investigations together and also their own studies. I would like you to know we are all working very hard to make a big dent on the tough shell of this dreaded disease.

Hiroshi Mitsumoto, MD

Volunteering at Columbia's MDA/ALS Research Center



by Meredith Pasmantier

As a premedical student at Columbia University on the Morningside Campus, I was eager to find a volunteer opportunity in a clinical research setting that would complement my coursework. A friend of my grandmother's had suffered from ALS and had considered traveling all the way from Florida to New York because she had heard about the exciting research being conducted at the ALS Center at Columbia. Hearing her story prompted me to contact Dr. Mitsumoto who was kind enough to welcome me as a volunteer this past September.

On my first day, I was paired to work with nutritionist and research coordinator, Kate Bednarz. I remember being a little concerned that my lack of previous experience might make it difficult for those assigning me a task. But Kate immediately put me at ease and did a great job of explaining some of the complicated research projects in a way that I could understand. My first job was to enter data from patient interviews into the computer system. It proved to be a valuable introduction to the basic symptoms and progression of ALS.

Soon after, Dr. Mitsumoto introduced me to Dr. Woo-Kyung Kim, a research fellow from Korea, and gave me the opportunity to assist her in the

beginning stages of her current work. Dr. Kim is exploring the differentiation between Progressive Muscular Atrophy (PMA) and ALS, by combing through hundreds of patient files that may elucidate the relationship between these two diseases. She too was very patient with my "Introductory Biology" level of knowledge and even took the time to draw diagrams as she explained the complexities of her research.

In fact, as I became better acquainted with the rest of the clinical staff members over the following months, I was pleased to discover that they were all equally welcoming and more than willing to take the time to teach me about their work.

Perhaps the most rewarding of my time as a volunteer so far was when I had the chance to observe during a clinic day. A patient and her husband generously allowed me to sit in with them over the course of several hours as the entire clinical team rotated through. I was very impressed by all that the ALS Center has to offer in a single patient visit. Not only was she seen by her neurologist, but also she was able to receive prompt advice from a pulmonologist, gastroenterologist and nutritionist. When she met with the physical therapist, she was told that she could benefit from a better leg brace. I was impressed that an orthotist was immediately available to fit her for a new brace. Most of all though, I was inspired by the courage of the patient herself. I cannot imagine the physical and emotional toll this disease must take on those afflicted by it, and I also cannot imagine anyone handling it with more dignity and grace.

At this point on the path to becoming a doctor, most of my time is spent in the lecture hall or the library. Each week, I look forward to my time at the ALS Center because it reminds me of why I chose to pursue this career in the first place. I have a long road ahead before reaching my goal, but my experience as a volunteer assisting with research and observing patient visits serves as a reminder that it is certainly worth it.



CURRENT CLINICAL TRIALS

Actively Enrolling:

- Dextromethorphan/Quinidine (DMQ) in the Treatment of Pseudobulbar Affect in ALS
- 2-Part, Randomized, Double-Blind, Safety and Tolerability Study Evaluating KNS-760704 in Patients with ALS
- Exercise and Oxidative Stress in ALS
- Genetic and Epidemiology Study
- Ambispective case-control study of oxidative stress
- Skin and ALS
- Non-Invasive Ventilation

Ongoing (closed to enrollment):

- Stage II Early Treatment of ALS with Nutrition
- Skin Biopsy

Upcoming Summer/Fall 2008:

- Clinical Trial of Ceftriaxone in Subjects with ALS
- Arimocloamol in ALS
- Talampanel in ALS

Completed:

- Modafinil for Fatigue in ALS
- Clinical Trial of High Dose CoQ10 in ALS
- Longitudinal study of Cognitive Function in ALS

Please call Kate Bednarz

at 212-305-2027 for more information.

LITHIUM IN ALS by Jinsy Andrews, MD

Investigators in Italy at the University of Pisa (Fornai et al, 2008) proposed that lithium promoted autophagy which is a mechanism for digestion of cell contents by enzymes within that cell. They believed this process may be involved in ALS. Prolonged survival in mouse models of ALS prompted the scientists to do a small pilot study in ALS patients. They conducted a small study with a total of 44 patients with early ALS. Sixteen were randomized to receive lithium and riluzole and 28 continued to take riluzole only. At the end of 15 months, none of the patients taking lithium died compared to almost 30% of the patients taking riluzole alone.

These unprecedented results circulated quickly among the ALS community and many internet forums such as "Patients Like Me", "People with ALS (PALS)" and others. Although these findings are dramatic and exciting, many researchers are cautious because the number of patients in the study were small and results can be easily skewed by many different factors. Additionally, lithium has significant side effects including seizures, tremors, fatigue, and cognitive problems among others. The effect of the

New ALS Biomarker Study Open for Enrollment

by Harvey Arbesman, M.D.

There is a great need for a reliable and easy to use method to assess the progression of Amyotrophic Lateral Sclerosis (ALS) in order to accurately monitor both the disease and efficacy of treatment.

It has been noted in the medical literature that even when ALS patients are immobile at the terminal stage, they do not develop bedsores as would be expected. The skin of ALS patients has also been described as being supple and as having reduced elasticity. It is possible that these skin changes correlate with the extent and severity of neurological disease since many of the underlying biochemical and structural changes found in the skin of ALS patients are correlated with disease duration.

The purpose of this research study is to determine whether measuring changes in the elastic properties of the skin through the use of a Cutometer® can serve as an indirect measure of the progression of ALS. The Cutometer® is a minimal risk device that measures the elasticity of the skin through a gentle, painless, suction on the skin.

In this study, the changes in the elastic properties of the skin as measured by the Cutometer® will be compared to changes in the neurological function of the patients. Recordings will be taken by study staff trained in the use of the Cutometer® on the inside surface of the subject's forearm and lower back. The spouses of patients enrolled in the study will be asked to serve as controls and they will also be measured using the Cutometer®. Participants (enrolled patients and spouses) will be followed at each regular visit at the Center (approximately once every 3 months) for a maximum of 6 months. Changes in the Cutometer® readings over the 6 month period of measurement will be compared between ALS subjects and controls and we will examine the data to see if Cutometer® readings correlate with changes in neurological function over the same 6 month period.

medication can also be unpredictable when combined with other medications, supplements, or other medical conditions, especially if it is not properly monitored.

This study has prompted ALS researchers to initiate formal clinical trials quickly. There are multicenter natural history-controlled and randomized, placebo-controlled trials are on the way. Our center has begun conducting a small safety study of lithium and plan to be involved in the larger trials planned.

Reference:

Fornai F, Longone P, Paparelli A, et al. Lithium delays progression of amyotrophic lateral sclerosis. *Proceedings of the National Academy of Sciences* 2008; 105: 2052-2057



CoQ10 Trial Results

From the Desk of Dr. Kaufmann



CoQ10 is not promising enough to warrant further study as a treatment for ALS – Early Results from the “Clinical Trial of High Dose Coenzyme Q10 (CoQ10) in ALS - QALS”

Thanks to the participation of 185 people with ALS and the contributions of nineteen ALS research teams across the United States, we are now able to report the results of QALS. The trial was a successful collaborative effort between researchers, clinicians and people with ALS in that we met our recruitment targets and completed the trial in a timely fashion.

CoQ10 is a promising treatment for ALS because it is a mitochondrial co-factor and powerful antioxidant. Mitochondria are the “powerhouses” of the cell, and they are thought to have impaired function in ALS. Free radicals that can be neutralized with antioxidants are also thought to play a role in ALS.

We therefore conducted a Phase II clinical trial, funded by the National Institute for Neurological Disorders and Stroke. We wanted to find out if it is worthwhile pursuing CoQ10 as a treatment for ALS in Phase III. Our trial was not designed to definitely answer the question if CoQ10 is actually beneficial in ALS. Only a Phase III trial can show this. You may ask why we did not start a Phase III trial right away. The reason is that Phase III trials are very large, expensive and take a long time. When there are several new drugs on the horizon, it is an efficient strategy to test some of them in Phase II so that we can have at least preliminary answers more quickly and without using up all the resources.

The results for our primary outcome suggest that CoQ10 at 2700 mg daily is not promising enough to warrant further studies as a treatment for ALS. The difference between the CoQ10 group (2700mg daily) and the placebo group was not large enough to suggest that one would find a meaningful difference in a future Phase III trial. Our study did not address the question of whether CoQ10 may be promising in combination with other approved or experimental drugs, but usually the first step in assessing combination therapies is to investigate the efficacy and safety of the individual compounds.

Although this result is disappointing because we did not find a drug that helps people with ALS, it is in a way positive that we were able to obtain this information. The reason is that many people with ALS think that they have to buy CoQ10 and that it will help them. Now, we know this may not be worthwhile based on our results showing that it is unlikely that there is more than a small effect. Also, we think that our study helps the ALS community. This is because we conclude that larger studies with CoQ10 at 2700mg daily are not warranted. Therefore, other drugs that are more promising can be tested as no further resources will have to be used to test CoQ10 in ALS.

We want to thank NINDS for funding, and the investigators for their support and their contributions to this trial. Most of all, we want to thank people with ALS and their caregivers who have participated and generously given their time and effort. Clinical trials can not only benefit those who directly participate, but they can help others with ALS. Clinical trials allow us to rationally test treatments, eliminate harmful or ineffective treatments rapidly, and, hopefully, find an effective and safe treatment for ALS soon.



ALS and Hospice

Living with an illness that strongly impacts one's ability to function independently can challenge the strongest among us. Providing care for a person living with ALS can be a daunting experience, especially in a world in which most of us also work outside of the home. As a social worker, working with families living with ALS, I have learned that success stories often reflect the family's willingness to accept care and support from outsiders. This can come from an informal network of caring friends and neighbors or in the form of a paid helper who relieves the family caregiver for a few hours, or lives-in to provide round-the-clock care.

Another important source of assistance in caregiving is hospice. I am aware that many of us respond to this word with fear, defaulting to our association of the word "hospice" with the phrase "less than 6 months of life to live". This is not a true picture of what hospice can be for those living with ALS. Here is the picture of hospice from my perspective as a hospice social worker.

First of all, let's review what the hospice program is and is not. A diagnosis of ALS entitles a patient, who is then considered "disabled" according to Federal standards, with access to health care under the Medicare program. Hospice is a benefit program of Medicare, and is supported by many private insurance companies as well. Hospice is free to those who qualify and provides a myriad of important support services for both patients and family members living with ALS.

So how does one qualify? Hospice is a program that is available to people who no longer have "treatment options", such as surgery or chemotherapy to halt their disease process. Initially used for the most part by patients with cancer, hospice qualification is where the words "less than six months to live" originated. Physicians recommending patients to hospice are asked to use a set of specific markers within each disease group to attempt to document that patients have a limited remaining lifespan. The good news with ALS is that because this disease is so individualistic in its presentation, the government's devised markers often apply initially to a particular ALS patient, but the timeframe of the diseases progression does not. I have had many, many patients who qualified by the standard markers, came on to hospice and remained there for a long time beyond the six months. Once qualified, patients with an ALS diagnosis are entitled to remain on hospice as long as it is useful to them, even if that is a year or even two!

To me, the term "less than six months" is not a true depiction of what to expect when it comes to ALS patients on hospice, but that said, families who are approached by their doctor or other healthcare professionals as "appropriate" for hospice have to be ready emotionally to come on to the program. Postponing hospice, because one fears that you are starting the "six month" clock, means living without some wonderful services that you are entitled to have. Often it is those families who have had previous positive experience with the benefits of this program who can embrace hospice early on.

Once hospice is begun you will suddenly be a part of a wonderful process. Hospice is an interdisciplinary team approach to care, available to you 24 hours a day, seven days a week. As you work with the hospice team you will still have control over decisions about your life and your

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ALS and Hospice (continued from page 6)

care. You will also retain a relationship with your primary care physician. Visiting team members include; the nurse, who examines the patient each week to monitor the patient's condition and to provide appropriate care to maintain the patient's comfort; a social worker who works with both the patient and the family members to insure that they are coping with the challenges of life; chaplains who assist in the religious and spiritual needs of the family; home health aides who help with the physical needs of the patient and trained volunteers who lend a hand in enhancing the family's quality of life. That is really what hospice is about. It is the provision of palliative (reduction of suffering) services and medical support to help families live with the highest quality of life available, during the end course of an illness.

Doctors often recommend a particular hospice at the time of qualification but each family can select the hospice of their choice, since there are numerous companies who provide hospice services and as the consumer you are the one who should choose the one that is best for you. The services that each provides will vary, with some providing two hours of nursing aid care for five days a week and others providing 4 hours for seven days a week. Families can ask for hospice teams to make a presentation to them before they enroll, during which you can ask specific questions about what supplies they make available and if they have any special services such as massage therapy or aroma therapy, etc. In most hospices medical supplies and prescriptions are delivered directly to your door.

Family plays an important role in hospice and a designated family member or close friend will serve as the hospice contact person. Because hospice takes place anywhere that people call home, hospice team's work in private houses, apartments, nursing facilities and hospitals. There are still some free standing hospice facilities but they are primarily used by those who are very close to the end of life.

Hospice is a palliative care service designed to enhance life's quality, reduce the pain and suffering of diseases such as ALS, and help families cope with the challenge of caregiving. Hospice helps families to celebrate and live life to its fullest. It is the family who defines what their needs are and hospice's role to respond to those needs. Hospice can greatly enhance your life... if you let it!

Toby Tider, LSW, MSW,
Evelyn Richardson, RN
Family Choice Hospice
(732) 396-1200

Thank you for those who participated in the Exercise and Oxidative Stress Study in ALS!

We hope to recruit 10 additional subjects in the next few months towards this pilot study. If you are interested in learning more or participating in this study, please contact me at achen@neuro.columbia.edu.

Since the Fall of 2007, we have recruited 14 subjects from our ALS center for this pilot study. Your participation allows us to investigate the physiological and oxidative stress responses in ALS patients and control subjects following a regular cardiac stress test (see <http://www.columbiaals.org/research/exercise.html> for further details). It is with studies like this one that we hope to further our understanding in the causes and progressions of ALS, and to identify potential biomarkers that may ultimately lead to or guide the development of a treatment.

Lastly, we are grateful to the Judith and Jean Pape Adams Charitable Foundation, Spina Family Golf for Life, Ride for Life, and the Bowen Gold Outing for their continued support in this innovative and exploratory study.



The Eleanor & Lou Gehrig MDA/ALS Research Center
Division of Neuromuscular Diseases
Columbia University Medical Center

*Special thanks to the
**MDA/ALS Division for their
 continuing support of our
 patients and their caregivers.***



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On March 2nd through 3rd the investigators of the Safety and Tolerability Study Evaluating KNS-760704 in Patients with ALS met in Philadelphia to kick off the start of the trial. The team of investigators pictured above is on the steps of the Philly Art museum doing the infamous 'Rocky' pose, as a representation of their future triumph over ALS.

In this issue:

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MDA/ALS Educational Support Groups:

New York City

All Souls Unitarian Church
 1157 Lexington Avenue
 (between 79th & 80th)
 New York City
 First Floor
 Please join us
 Fourth Monday of each month
 6-8 p.m
 For more information contact
 Jacqueline Puerta: 212-689-9040

Northern New Jersey

Jewish Community Center
 on the Palisades
 411 E. Clifton Avenue
 Tenafly, NJ 07670
 Please join us
 Third Thursday of each month
 4-6 PM
 For more information contact:
 Maywood Center: 201-843-4452

Westchester

Burke Rehab Center
 (Clock Tower Bldg, Rm 202)
 785 Mamaroneck Ave
 White Plains, NY
 Please join us
 Second Thursday of each month.
 6-8pm
 For more information contact
 Gloria English: 914-345-5062

Long Island

St. Charles Hospital
 200 Belle Terre Road
 Port Jefferson, NY 11777
 Please join us
 First Friday of each month
 4:30- 6:30 PM
 For more information contact
 Deidre: 631-582-7761

Editor
 Olena Jennings



The Eleanor and Lou Gehrig
 MDA/ALS Research Center
 of Columbia University Medical
 Center gratefully acknowledges
 the patients and families who
 have contributed financially to
 the publication of the ALS
 Newsletter.