

In robotics study, gains seen even years after stroke

A VA study that used robots to deliver high-intensity therapy has provided strong new evidence that people can gain back function even years after a stroke. The study appeared online April 16 in the *New England Journal of Medicine*.

“There are nearly six million stroke patients in the U.S. with chronic deficits. We’ve shown that with the right therapy, they can see improvements in movement, everyday function and quality of life,” said study chairman Albert Lo, MD, PhD, a neurologist at the Providence (R.I.) VA Medical Center.

The three-year study enrolled 127 Veterans at four VA sites. All had suffered a stroke at least six months earlier and had

see **STROKE** on pg. 4



Stroke patient Benson Belo uses a robot called the MIT-Manus at the Baltimore VA Medical Center. The system allows for high-intensity therapy that helps restore strength and function to stroke-affected limbs.

Photo by Mitch Minkin

VA space experiment among last to fly on Discovery shuttle

She calls them her “astromice.” Former astronaut Millie Hughes-Fulford, PhD, a cell biologist with VA and the University of California, San Francisco, sent 16 mice into space aboard the Discovery shuttle on its April mission to the International Space Station. The shuttle, first flown in 1984, and

two others are being retired later this year. Hughes-Fulford and her team at the Laboratory of Cell Growth are studying the mechanisms behind the effects of space on the immune system.

NASA first learned about the effects of spaceflight on T cells—key in fighting infections—back in the 1970s. “Basically, what happens is the T cell does not activate—it doesn’t respond to an antigen presentation,” says Hughes-Fulford. “When the astronauts come back to earth it doesn’t go back to normal for about seven days.”

Unlike the effects on bone mass, the changes to astronauts’ immune systems gradually reverse—even after long space flights. But learning why the changes occur in the first place could lead to new treatments for earthbound humans with immune disorders and new therapies to fight pathogens, says

see **SPACE** on pg. 8



Photo courtesy of NASA

This image of the underside of Discovery, with the Caribbean in the background, was taken last month from aboard the International Space Station.

‘Dr. Brain Dude’

Dr. Russell Buono is on a mission to teach kids neuroscience

Neuroscientist Russell J. Buono, PhD, grew up in a blue-collar family and earned his way through college and graduate school as a meat cutter. Today, working from his lab at the Coatesville (Pa.) VA Medical Center, he is a top figure in research on the genetics of epilepsy. Among local students, though, he is better known for the hands-on brain exhibits he brings to schools and colleges throughout the area.

“It happens all the time,” says Buono. “I’ll walk into the ice cream parlor with my family and some kid will recognize me. Last time, a girl looked at me and said, ‘I know you, you brought a brain to my class when I was in the 7th grade. I never forgot that. I’ve been so interested in science ever since.’”

Buono also used to do educational outreach in Ohio, where he worked before arriving in Coatesville in 2006. It was there a 6th-grader dubbed him “Dr. Brain Dude”—the title he’s most proud of, he says.



Dr. Russell Buono directs the Golden Brain Bank at the Coatesville (Pa.) VA Medical Center, a rich resource for neurology researchers, and has conducted educational outreach for more than 15 years.

In 2000, Buono cofounded Brain Awareness Week at the Franklin Institute. Hosted each spring by the Philadelphia Society for Neuroscience, the event features a “human brain bar” where kids touch and hold preserved brains. To learn about protecting their skulls, they get to put a raw egg in a Ziplock bag and crash it on the floor. “They like that, as you might imagine,” says Buono. Volunteers then fit the eggs with miniature bicycle helmets. “We let them throw it on the floor, smash it against the wall, kick it, and they can’t break the egg.” To complement the activity, the Brain Injury Association of Pennsylvania gives away hundreds of free bicycle helmets. As a more serious follow-up, Buono shows a video of a boy who sustained a traumatic brain injury after a bicycle accident. “We illustrate the point with kids that they really should be protecting their heads,” says the researcher.

VA Research Currents spoke with Buono to learn more about his educational outreach and the brain collection at the Coatesville VA.

RC: Today there’s so much science-education material on TV and the Web. Are in-person, hands-on science exhibits as valuable as they once were?

RB: It’s the same argument you’d make concerning medical education for doctors. Do you want people to learn about anatomy virtually—totally through a computer—or is it beneficial to have your future physicians actually touch the real material? Seeing images is great. It can teach you a lot. But it’s very different to hold the actual material and to have someone right there to answer your questions.

RC: How do kids react to seeing and touching a real human brain?

RB: When we’re in an environment where it’s school kids and their chaperones, the kids are much more willing to look at the photo [of a fresh, raw brain] for what it is and then put on some gloves and hold the preserved material. The older we get, the more we face our own mortality. When you’re a kid, you don’t think in those terms.

VA Research Currents

is published 10 times per year for the Office of Research and Development of the U.S. Dept. of Veterans Affairs by VA Research Communications

103 S. Gay Street, Rm. 517
Baltimore, MD 21202
(410) 962-1800, ext. 223
research.publications@va.gov

Editor: Mitch Mirkin

The information in this newsletter is not intended as medical advice and should not be used to diagnose or treat any condition.

Veterans Health Administration
R&D
www.research.va.gov

see **BRAIN** on next page

The brain up close—Dr. Heather Basehore, a brain researcher at the Coatesville VA Medical Center and colleague of Dr. Buono's, shows a preserved human brain to student Maliya Majors. The exhibit was part of a recent "Take Your Child to Work Day" at the center.



Photo by Tommy Leonardi

BRAIN *(from previous page)*

RC: What types of questions do you get from kids?

RB: A lot of them ask whether it's real, because our preservation technique makes the brain look a bit clay-like and stiff. Sometimes they'll ask where we get the brains from. The real answer is, from folks who have donated their body for medical science. But when the kids are kind of unruly, I tell them we get the brains from really bad 14-year-olds.

RC: What are some basic facts people learn from the exhibits?

RB: The first thing that strikes most people is the scale. They think their brain and spinal cord are a lot bigger than they really are. When they see the actual specimens, they can't believe it. They also come away knowing what their spinal cord looks like. Everybody thinks that row of bones going down their back helps them stand up straight. They walk away understanding that those bones are really there to protect that cable, the spinal cord. They see the cable itself, how small it is, and that impresses them.

RC: Do you talk about diseases of the brain?

RB: Part of our brain collection deals with pathology. We have brains that were affected by Alzheimer's, Parkinson's, multiple sclerosis, Huntington's, brain tumor, stroke. Most people who walk by the table know someone who suffered one of these things. We also have the brain of someone who died from a subdural hematoma after a fall. I have the blood clot in a jar, which is quite graphic. You can see how the blood clot deformed the brain to the point where it caused death.

RC: Tell us about the brain collection at the Coatesville VA.

RB: Dr. Greg Golden [of the Coatesville VA] was a good friend and collaborator. He initially started doing autopsy work in the 1980s and did about 350 brain autopsies. We have almost all those brains represented here in material that is fixed in formaldehyde and stored in a detergent solution to keep it from getting moldy or infected. From about half the brains, we have material that was never fixed, stored in -80 degrees Celsius freezers. That tissue is very valuable. Greg passed away in 2005, and I was recruited to oversee the brain bank in his place. We named it the Golden Brain Bank in honor of my old friend.

RC: What makes the brain tissue in the bank so valuable for research?

RB: VA has always been ahead of the curve in terms of electronic medical records. So we've got brain tissue from folks 15 years ago and we have their complete medical histories—whether they smoked, what diseases they had, what medications they took. That information is very useful to researchers. In addition to VA groups, we have investigators at several universities who withdraw the tissues for their studies on schizophrenia, substance abuse, epilepsy, Alzheimer's disease and other conditions. And so from a central location, from the donations our Veterans made years ago, many scientific publications on different aspects of brain disease will start to flow. I know my old friend Greg would be proud for sure. —

STROKE *(from page 1)*

moderate to severe impairment of an arm. In most cases, the strokes had occurred several years beforehand—even as far back as 1980, in one case. Patients typically get rehabilitation therapy only during the first six months or so after a stroke. Conventional thinking has been that further therapy offers little benefit. Studies in recent years, though, have begun to suggest otherwise.

Improvements seen in everyday function

The therapy in the VA study was repetitive, guided movement, three times a week for three months. One group of patients did the therapy with the use of robots designed at the Massachusetts Institute of Technology. Others did similar high-intensity exercises with a therapist. A third, smaller group had only “usual care”—they received general health care but no specific therapy for their stroke-damaged limb.

The two therapy groups showed improvements in arm movement and strength, everyday function, and quality of life. The gains began slowly during the initial three-month therapy period and continued to grow over the next six months, even after

therapy had ended. At nine-month follow-ups, the gains for the two therapy groups were still modest but were statistically and clinically significant, says Lo.

To measure the impact on everyday life, researchers asked patients a battery of questions: for example, how well they could cut food with a fork and knife, open jars or tie their shoes. The patients were also asked about activities not directly related to their arm, such as walking or stair-climbing. Most patients in the two therapy groups reported across-the-board progress, compared with no progress in the usual-care group.

Lo’s team theorizes that boosting arm function helped patients be more active overall, which led to wider health improvements. “We believe that by getting better control of their arm, they were able to achieve more balance and mobility in general,” he said.

Usual-care patients were offered the intensive therapy after the study ended, so they too could benefit from it.

The VA study featured a robot called the MIT-Manus, which had been tested in a few smaller trials. Users sit at a table with their weakened arm attached to the device. They follow prompts on the screen—or

Study at a glance

- The study included 127 Veterans at the VA medical centers in West Haven, Baltimore, Gainesville and Seattle.
- Participants’ average age was 65. About 96 percent were men; 78 percent were white. About a third had suffered multiple strokes.
- Veterans who received intensive arm-movement therapy for three months—either guided robotically or by a therapist alone—maintained modest but significant improvements in arm strength and movement, everyday function, and quality of life at nine months.

instructions from a therapist—and try to perform a task with their arm. The robot senses their movement and helps as needed.


“These are video-game-like tasks,” said George Wittenberg, MD, PhD, the study’s lead investigator in Baltimore. “The patients are moving a cursor from one place to another, or guiding a symbol on the screen through a maze, and using their arms to control the movement of the cursor. The robots provide ‘power steering’ for the

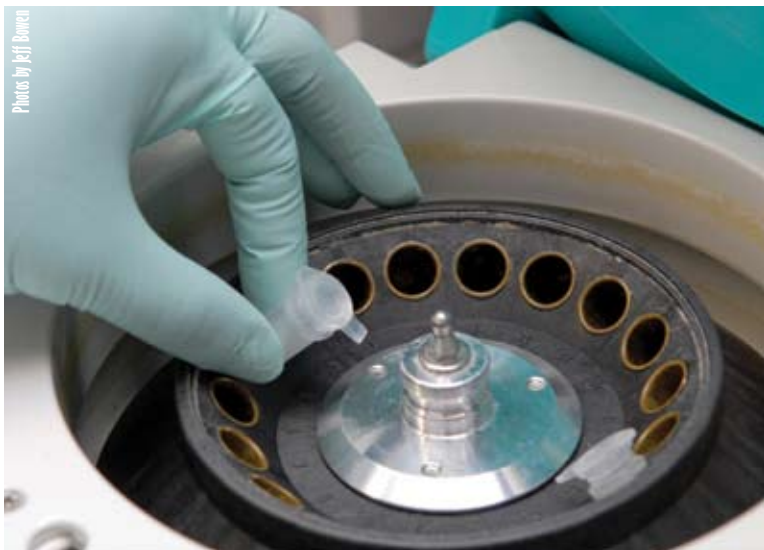
see **STROKE** on pg. 8



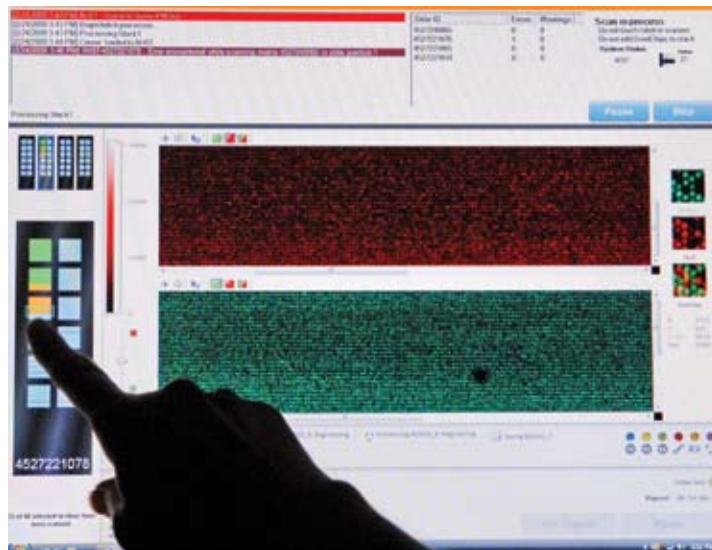
Geriatrician Dr. Lenise Cummings-Vaughn (second from left) meets with prospective participants in a memory study at the St. Louis VA GRECC.

Geriatrics conference set

Maintaining a healthy brain, the impact of oral diseases on older adults, spirituality and dementia, new and emerging therapies for Alzheimer’s disease, optimizing homecare, stress and the aging process—these are among dozens of topics to be covered at the 21st Annual St. Louis University Summer Geriatric Institute, to be held June 1 – 2, 2010, in conjunction with the Geriatric Research, Education and Clinical Center (GRECC) at the St. Louis VA Medical Center. The program is designed for health professionals in geriatrics and gerontology. The overall goal is “to provide participants with up-to-the-minute information about geriatric care and social issues affecting the well-being of older adults.” To learn more, visit <http://medschool.slu.edu/cme>. 



Photos by Jeff Berens



Genomics research—phases of which are pictured here—by VA and collaborating institutions is seeking genetic clues to Lou Gehrig's disease, or ALS.

Study finds some evidence of ALS link to head injury

DNA analysis suggests association stronger in those with APOE-4 gene

One of the first published analyses from a study of genetic and environmental risk factors for amyotrophic lateral sclerosis (ALS), or Lou Gehrig's disease, suggests that prior head injury may double the risk for the condition. The link was strongest for those with a gene known as APOE-4, which is also a risk factor for Alzheimer's disease.

A team at the Durham VA Medical Center and Duke University, led by Silke Schmidt, PhD, compared questionnaire and

DNA results from 241 Veterans with ALS and 597 without the disease.

According to VA physician-researcher and study co-author Eugene Oddone, MD, MHSc, the questionnaires probed Veterans' health histories and behaviors extensively. The interviews sometimes took up to four hours. The Veterans who participated were part of a VA registry that was started in 2003 and enrolled 2,089 patients with ALS through 2007. Of those, about three-quarters provided blood samples for DNA analysis.

Oddone says a link between ALS and head injury has emerged, so far, in only one other study. "An Italian group had a study on soccer players that found about a twofold increase in risk," he says. But he points out that while the medical literature on boxers, football players and other athletes prone to head injuries is replete with findings on

dementia and Parkinson's disease, no other studies in those populations have shown a link to ALS. "No one has found increased ALS in boxing or football," says Oddone.

A few studies have linked ALS to military service in general—though the reasons for the connection are still unclear—and VA extends service-connected disability ratings to all Veterans with ALS, regardless of when and where they served. According to Oddone: "Most scientists think ALS risk is more complicated than strictly having served in the military. It's probably a combination of susceptibility genes, exposures, and then maybe something down the line that triggers the onset." The strongest risk factor, he says, is age—the older the person, the higher the risk of ALS.

He says further analyses by the VA-Duke group may reveal other genetic or environmental factors in ALS. "I'm hopeful the work will help link exposures to increased susceptibility," remarks Oddone.

see **ALS** on pg. 8



Photo by Warren Parth

Vietnam-era Veteran Ralph Covington of Pittsburgh, being comforted here by his wife, Annetta, volunteered for a VA study on the genetics of ALS. "I want to help find a cure for it," he says. "I want to help somebody else if I can."



Photo by Michael Moody

Veteran Eldon Cannon, 71, has his hearing checked by Dr. Melissa Teahen, an audiologist at VA's National Center for Rehabilitative Auditory Research at the Portland VA Medical Center.

Nurse practitioners rate high among VA patients

—Surveys completed by 1.6 million users of VA health care show that patient satisfaction goes up more when the number of nurse practitioners at a VA facility is increased, versus when the number of physicians or physician assistants is increased. According to the authors, led by Dorothy Budzi, DrPh, the study shows that “a majority of primary care clinic patients prefer to see nurse practitioners as compared with physician assistants and physicians.” They point out that nurse practitioners focus on health promotion, disease prevention and health education, and tend to use more counseling techniques in their sessions with patients than do the other two disciplines. As such, say Budzi and colleagues, “Physicians and PAs should be educated on these characteristics to promote patient satisfaction and expected outcomes.” (*Journal of the American Academy of Nurse Practitioners*, March 2010)

‘Orphan’ cancer drug may have more uses

—A drug that has shown promise in early clinical trials for breast and ovarian cancer, as well as multiple myeloma, may also be an effective agent against a common type of esophageal cancer, suggests a study at the Kansas City (Mo.) VA Medical Center. The drug, 2-methoxyestradiol, known also as 2ME2 or by the trade name Panzem, is a naturally occurring derivative of estrogen. It causes cancer cells to self-destruct through a process called apoptosis and also blocks the formation of new blood vessels that feed tumors. It was given “orphan status” by the Food and Drug Administration in the past so it could be developed to treat multiple myeloma and ovarian cancer. In the new VA study, scientists identified the pathways through which the drug acts on Barrett’s esophageal adenocarcinoma cells. Senior author Sushanta Banerjee, PhD, points out that this cancer affects fewer women than men, possibly because 2ME2 is produced at higher levels in women’s bodies. (*Molecular Cancer Therapeutics*, March 2010)

Routine hearing screening—A study of 2,305 older Veterans at the VA Puget Sound Health Care System found that those who underwent routine hearing screening when they sought general medical care were about twice as likely to be using a hearing aid one year later, compared with Veterans who had not undergone such screening. Not surprisingly, those using hearing aids reported significant improvements in everyday function. Currently, VA does not provide routine screening for hearing loss, although all VA medical centers and many VA community-based outpatient clinics have audiology clinics, and VA primary care or specialty physicians commonly refer patients for hearing evaluations. (*Journal of the American Geriatrics Society*, online March 11, 2010)

Study supports use of advance directives


—A study of more than 3,700 older adults who died between 2000 and 2006 found that a majority of those who needed to have medical decisions made for them at the end of life had advance directives in place, and that those with advance directives were more likely to receive end-of-life care in line with their preferences. Advance directives include living wills, which state preferences for life-sustaining treatment; and durable powers of attorney, which designate surrogate decision-makers. Of 3,746 people in the study, more than 25 percent needed treatment decisions made but were unable to do so on their own. Of these patients, 68 percent had advance directives. According to the study, 95 percent of the older adults who requested limited care and 96 percent of those who requested comfort care received care that matched their preferences. The authors, from VA’s Center for Clinical Management Research in Ann Arbor, conclude, “Advance directives are important tools for providing care in keeping with patients’ wishes.” (*New England Journal of Medicine*, April 1, 2010)

Protein test may help predict breast cancer spread

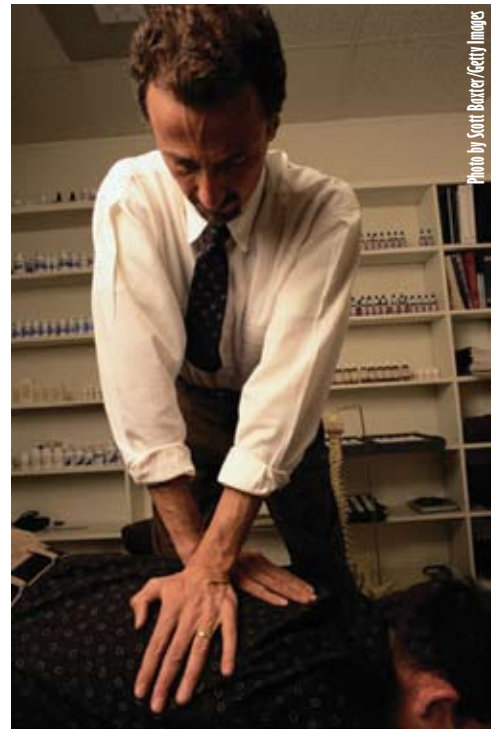
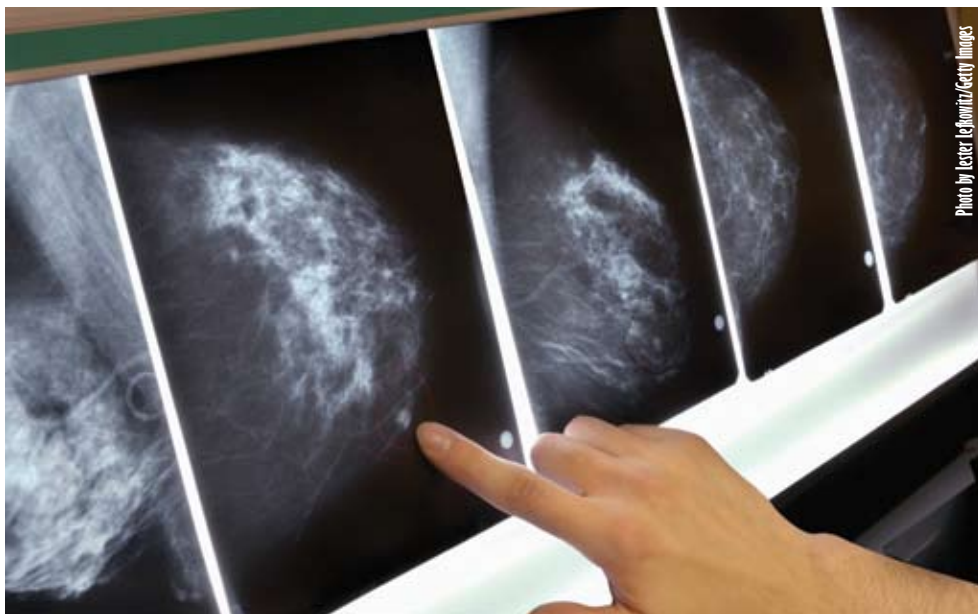
A team led by researchers with VA and the University of California, San Francisco, reported that a lab test for three proteins may help predict when ductal carcinoma in situ (DCIS)—a common noninvasive type of breast tumor—will lead to more serious, invasive breast cancer.

DCIS is usually detected by mammogram. It doesn't spread and isn't life-threatening, but many patients pursue aggressive treatment to prevent the possibility of more serious tumors developing. "In the past, women were told they had a certain risk of developing further tumors, but could not be told whether they were at risk of an invasive cancer or DCIS," notes lead author Karla Kerlikowske, MD, co-director of the Women Veterans' Comprehensive Health Center at the San Francisco VA Medical Center and a professor of medicine, epidemiology and biostatistics at UCSF. "Risk of further tumors was lumped together into one risk group." In the face of this uncertainty, about 35 percent of DCIS patients opt for a lumpectomy alone; about an equal number for lumpectomy plus radiation or hormone treatment or both; about 25 percent for a complete mastectomy; and some 3 to 5 percent for active surveillance.

The new study looked at clinical outcomes and molecular markers in biopsied breast tissue from 1,162 women who had received a diagnosis of DCIS between 1983 and 1994 and were treated with lumpectomy alone. Of these women, 170 went on to develop invasive breast cancer over an eight-year period, and 154 faced another bout with DCIS. The researchers found that women whose initial DCIS lesions were detected by palpation—touch— or whose biopsied tissue expressed a combination of three proteins—p16, Ki67 and cyclooxygenase-2—were the most likely to develop invasive breast cancer. Other combinations of biomarkers identified those most likely to have a second incidence of DCIS. According to the study, patients in the lowest-risk category have only a two-percent chance of developing invasive cancer at five years and a four-percent chance at eight years.

If the new molecular screening methods are validated in further studies, says Kerlikowske, "Women will have much more information, so they can better know their risk of developing invasive cancer. It will lead to a more personalized approach to treatment." (*Journal of the National Cancer Institute*, online April 27, 2010) 

Ductal carcinoma in situ, a non-spreading form of breast cancer, is usually detected by mammogram.



Chiropractic treatment was introduced into the VA health system in 2004.

Chiropractic pain treatments for OEF/OIF Veterans

A preliminary study by chiropractor Anthony Lisi, DC, at the VA Connecticut Healthcare System found that 19 of 31 Iraq and Afghanistan Veterans with musculoskeletal pain who were referred for chiropractic care at the site reported an "important pain decrease" after the treatments. Any adverse effects of treatment were "mild and transitory." Before reaching the chiropractic clinic, most patients had tried several other treatment options for their musculoskeletal pain complaints. The analysis, albeit preliminary, is the first published study of VA chiropractic care for Veterans of operations Enduring Freedom and Iraqi Freedom, and one of the first studies in general on chiropractic outcomes in VA. The therapy was introduced in VA in late 2004. According to a 2009 article by Lisi and colleagues, there were fewer than 40 chiropractors practicing at VA clinics nationwide at the time, and the most common reason for referrals to VA chiropractic clinics was low back pain. (*Journal of Rehabilitation Research and Development*, Vol. 47, No. 1, 2010)

Inside: In VA robotics study, gains seen even years after stroke

ALS *(from page 5)*

“We’ll know in six or eight months if there’s a smoking gun.”

If no compelling results turn up, notes the VA researcher, the next step would be to collaborate with other scientists nationwide and worldwide who have data on large numbers of ALS patients. In particular, besides the VA registry, there are ALS databases at the National Institutes of Health, the University of Massachusetts and the University of Chicago. Oddone: “If the four groups can come together and pool their information, we can get the numbers up to 6,000 or 8,000, and that would add a lot of statistical power.” ➔

SPACE *(from page 1)*

Hughes-Fulford, who flew a Spacelab mission in 1991.

After the space mice returned from their two-week, six-million-mile trip on April 20, the researchers compared them with a control group, challenging the animals’ immune systems with a protein from egg whites and then running comparative gene scans to see which genes might be activated in one group but not the other. The analysis will take several weeks to complete. ➔



Photo by Tommy Lenardi

Boning up on the brain—Neuroscientist Dr. Russell J. Buono of the Coatesville (Pa.) VA Medical Center helps Nicholas Trego learn about the brain. For more on “Dr. Brain Dude,” see page 2.

STROKE *(from page 4)*

arms—just enough assistance to allow people to move.” He said the therapy takes advantage of neuroplasticity—the ability of the adult brain to “rewire” itself. When neurons die because of a stroke, other brain cells, prompted by assisted body movements, begin compensating for the lost function. The robotic therapy mimics hand-over-hand therapy, in which the therapist asks the patient to move his affected hand and then helps as needed. “The difference has to do with the intensity and the duration of therapy that’s possible with the robot,” noted Wittenberg. During each hour-long therapy session, patients in the study made hundreds of repetitive motions with their impaired arm.

Lo stressed that robotic therapy still requires supervision from therapists. “This study was not about robots versus therapists,” he said. “It was about therapists using robots or conventional methods. The therapist will never be out of the picture.” ➔