OCTOBER 2008

VA Research Currents

RESEARCH NEWS FROM THE U.S. DEPT. OF VETERANS AFFAIRS

VA to play role in Defense-funded research on PTSD, TBI

A physician-researcher with VA and the University of California, San Diego (UCSD), will lead a $60-million, five-year, multisite consortium funded by the Department of Defense Psychological Health and Traumatic Brain Injury Research Program to study posttraumatic stress disorder (PTSD) and traumatic brain injury (TBI), which affect significant numbers of combat veterans of the wars in Afghanistan and Iraq.

Murray B. Stein, MD, MPH, a professor of psychiatry and family and preventive medicine at UCSD and staff psychiatrist at the VA San Diego Healthcare System, will direct the effort, part of DoD's Congressionally Directed Medical Research Programs. At a news conference held last month to announce the project, Stein cited a report from the Institute of Medicine that underscored the need for more effective treatments for PTSD. He suggested the same could be said of TBI. "The [consortium] aims to contribute

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Photo by Spc. Harold Fields

Research aims to help combat troops—Troops such as these National Guard members serving in Afghanistan, as well as future military cohorts, may benefit from studies on PTSD and brain injury to be conducted through a new DoD-funded consortium.

At Baltimore VA, stroke recovery studied from many angles


Photo by Mitch Mirkin

Reggae music pulses through the large, brightly lit gym in the basement of the Baltimore VA Medical Center. About eight men and women, some holding canes, slowly make their way around the green and yellow oval track. Each step seems to demand effort and concentration for the members of the group, but they are making steady progress toward their goal: recovery from stroke.

The Stroke Exercise Club meets three afternoons a week as part of a study on whether group exercise, reinforced with a home-based regimen, improves balance, fitness, walking ability and quality of life for stroke survivors. Exercise physiologist Jeff Beans—who says the eclectic mix of music for the classes ranges from Bob Marley to Frank Sinatra—believes the group atmosphere

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Regaining movement—Veterans James McMahon (left) and Harry Young participate in the "Stroke Exercise Club," part of a study at the Baltimore VA on the benefits of group exercise for stroke survivors.

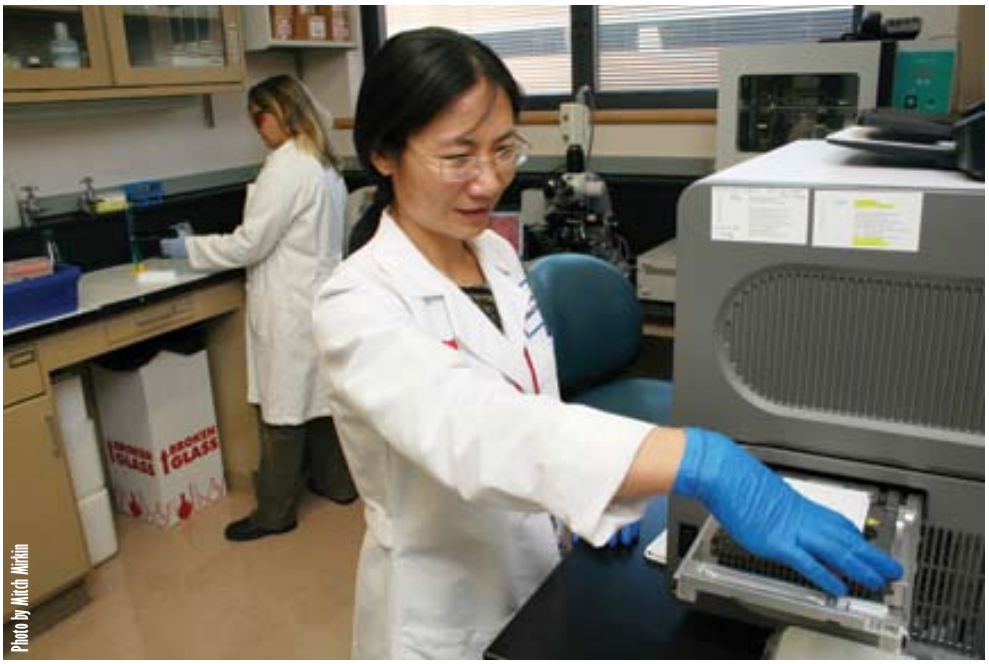
Photo by Mitch Mirkin

Probing the biology of stroke and exercise—As part of research at the Baltimore VA Medical Center on how stroke affects muscle tissue at the molecular level and how exercise can help reverse the effects, Dr. Guoyan Li performs a process known as PCR—short for polymerase chain reaction. Using samples of muscle tissue from stroke patients, the researchers can identify which genes are activated and measure protein levels.

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is "paramount" in helping older people regain function. Neurologist Richard Macko, MD, agrees: "It makes it fun, and the social reinforcement appears to sustain exercise behaviors in the elderly."

Macko heads the Maryland Exercise and Robotics Center of Excellence. The VA-funded program, which aims to improve fitness and movement and reduce disability for people affected by neurological illnesses, is a hub for stroke rehabilitation and research at the Baltimore VA and its academic affiliate, the University of Maryland School of Medicine. The program works hand in hand with VA's Geriatric Research, Education and Clinical Center (GRECC), directed by Andrew Goldberg, MD. The Baltimore GRECC is one of 20 such programs that VA supports nationwide.

Stroke studies link findings from lab, clinic, gym

Group exercise is one of the hottest topics under investigation by Macko and colleagues. Launched in 2003 through a collaboration with Italian stroke experts, the VA research effort examining this question will soon expand through partnerships with local senior centers and Veterans of Foreign Wars posts.

Other stroke researchers at the Baltimore VA, with funding from VA, the National Institutes of Health and other sources, are looking at issues such as the use of robots for stroke therapy, the effects of different types of exercise on walking ability, and the role of strength training in stroke recovery. Beyond the clinic and gym, stroke studies at the Baltimore VA also involve lab analyses of the genes and proteins involved in the disease. Biopsies of muscle tissue, for example, have pointed to a chemical called TNF-alpha as a possible cause of the wasting that occurs on the side of the body affected by stroke. "The damage of stroke is not all in the head—it's in the muscle also," points out Macko. Muscle tissue from a patient's affected side has up to three times more TNF-alpha than non-affected tissue.

TNF-alpha not only shrinks muscles—it also interferes with the action of insulin. That may explain the results of a 2006 Baltimore VA study, led by Macko's colleague Frederick Ivey, PhD, showing that more than three-quarters of stroke patients with paralysis on one side of their body have diabetes or a precursor condition called impaired glucose tolerance. "This is more than double the expected rates," explains Macko. "We believe it's because of these secondary biological changes in the muscle and the body composition that occur after a stroke."

Interestingly, diabetes is one of several diseases—including AIDS and cancer—that involve abnormally high levels of TNF-alpha in muscle tissue. "This is an ubiquitous molecular signal that appears to be related to these metabolic wasting

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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 R&D Communications

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Editor: Mitch Mirkin

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syndromes, including diabetes. And now we find it in stroke. It's a molecular smoking gun," observes Macko. His group is now exploring how exercise affects TNF-alpha levels: Can it reduce the protein to near-normal levels, and is that part of how exercise can help stroke patients regain function?

Exercise found to thwart diabetes in stroke patients

Related studies at the Baltimore VA are probing other biochemical effects of exercise—particularly its beneficial impact on insulin resistance and the risk of diabetes. Even as they continue to explore the exact mechanisms involved, Macko's team now has evidence, he says, that "treadmill aerobic training can improve glucose tolerance to prevent and even reverse diabetes in [the stroke] population."

In fact, exercise—both aerobic and strength training—is being validated in many studies as great medicine for stroke patients. Still, Macko doesn't rule out the possibility that his team may hit on a protein or other molecule that can be manipulated to achieve similar therapeutic effects.

Macko: "The question is, will we able to do what was done in rats and use pharmacological or genetic mechanisms to overexpress these molecules? It's conceivable that we could use these sorts of biological regulatory signals to help people even more than the exercise could or to help those who may be unable to train."

Taking advantage of 'neuroplasticity'

Future lab breakthroughs aside, Macko says one of the most exciting findings to date from studies by his group and others is that people can regain function even many

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Veteran Earl Elsey Jr., who suffered a stroke in 2004, uses a treadmill at the Baltimore VA.

Treadmill gains seen even decades after stroke

In a recent Baltimore-based study, people who walked on a treadmill even years after suffering stroke damage achieved major gains in fitness and mobility, reflecting actual "rewiring" of their brains. The study appeared online in the journal *Stroke* on Aug. 28 and will appear in the print edition in January 2009.

"Many stroke survivors believe there's nothing to be gained from further rehabilitation, but our results suggest that health and functional benefits from walking on a treadmill can occur even decades out from stroke. We believe exercise gives individuals a way to fight back against stroke disabilities," says Richard Macko, MD, of VA and the University of Maryland, lead investigator on the study. He noted that one of the patients in the study had significant improvement 20 years after a stroke.

Senior study author Daniel Hanley, MD, a professor of neurology at Johns Hopkins School of Medicine, added, "This is great news for stroke survivors because results clearly demonstrate that long-term stroke damage is not immutable and that with exercise it's never too late for the brain and body to recover."

The study involved 71 older men and women who had suffered a stroke an average of four years earlier. All the participants were tested for mobility and aerobic capacity, and a subgroup underwent functional magnetic resonance imaging (fMRI) to track brain activity linked to walking.

One group then took part in a treadmill-based exercise program, while the other group mainly did stretching, guided by therapists. After six months, walking speed for the treadmill group had increased 51 percent, compared with only about 11 percent for those in the stretching group. The treadmill exercisers were also more

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African Americans at greater risk for colon polyps—In a study of more than 85,000 patients who had colonoscopies, a team led by David Lieberman, MD, of the Portland VA Medical Center and Oregon Health and Science University found that black patients were at higher risk than white patients for serious colon polyps that could lead to cancer. The prevalence was particularly high among black women, who were 62 percent more likely than white women to have one or more large polyps. In light of the higher prevalence and mortality of colorectal cancer among blacks, some experts have theorized that blacks might be less likely to have early, detectable signs of the disease—such as large polyps—and may therefore not benefit as much as other demographic groups from preventive screening. Lieberman and colleagues said their results suggest otherwise and that the data strongly confirm the value and importance of screening colonoscopies for African Americans. (*Journal of the American Medical Association,* Sept. 24, 2008)

Older patients often want unnecessary tests—Researchers with the VA Outcomes Group, based at the White River Junction (Vt.) VA Medical Center and Dartmouth Medical School, posed hypothetical medical scenarios to 2,847 Medicare beneficiaries and asked whether they would want certain services—such as chest X-rays or visits to heart or lung specialists—to investigate their symptoms even if their regular doctor said the steps weren't necessary. Many of the respondents said they would in fact request the tests or referrals, notwithstanding their doctor's recommendations. The researchers concluded that "generalists striving to provide patient-centered care while at the same time limiting exposure to unnecessary medical interventions will need to address their patients' perceptions regarding the need for these services." (*Journal of General Internal Medicine,* Oct. 2008)

Compound may ease spinal-cord damage—Neurobiologists at the Kansas City (Mo.) VA Medical Center found that rats given a certain compound after sustaining a spinal cord injury had 50 percent less tissue damage in the spine than control rats. The experimental drug, which inhibits a gene called caspase-3, also enabled better functional recovery. The authors, led by Bruce Citron, PhD, suggest that "caspase-3 inhibition may be a viable therapy in the early hours" after spinal cord injury and that their results "may have significant implications for emergency management of human spinal cord injury." (*Spine,* Oct. 2008)

Race and colorectal cancer—Dr. David Lieberman of the Portland VAMC led a study on racial differences in the prevalence of colon polyps, which are often a precursor to colorectal cancer. *(See item at left.)*

Doctors often miss opportunities for empathy—A team with VA and the University of Rochester Medical Center found that in consultations with patients with lung cancer, physicians rarely responded empathetically to patients' concerns about mortality, symptoms or treatment options. The study, based on 20 recorded and transcribed visits, found that the doctors missed many opportunities to recognize and possibly ease their patients' concerns and provided little emotional support. The authors, whose findings jibe with those of past studies involving primary care doctors, oncologists and surgeons, say they hope the study will be useful in designing programs to improve doctors' communication skills. (*Archives of Internal Medicine,* Sept. 22, 2008)

Drug treatment of older veterans with PTSD found to be 'conservative, cautious'—Investigators with VA's New England Mental Illness Research, Education and Clinical Center analyzed the treatment records of nearly 245,000 veterans with posttraumatic stress disorder, all over age 45, and found that most were prescribed an antidepressant, sedative or antipsychotic drug. Medication therapy, however, tended to decrease with age, especially when the treatment was provided at VA mental health clinics, "perhaps reflecting the greater sensitivity of specialists to the risks of elderly veterans." Overall, concluded the authors, "Older veterans diagnosed with PTSD appear to receive conservative, cautious treatment." The study did not examine the use of other treatments, such as psychotherapy. (*American Journal of Geriatric Psychiatry,* Oct. 2008)

Putting polytrauma care 'on the map'

In a study to be presented at a national VA meeting in December, investigators at VA's Rehabilitation Outcomes Research Center (RORC) in Gainesville, Fla., used specialized geographic software to track access to VA care for traumatically wounded veterans of the Afghanistan and Iraq wars. The findings will help VA planners decide where to locate services for current and future cohorts of veterans.

The research, led by Diane Cowper Ripley, PhD, plotted the home ZIP codes, counties and regions of nearly 8,000 seriously wounded veterans—anonymous, for purposes of the study—who needed rehabilitation care during 2003 or 2004. That information was compared against the locations of VA facilities that deliver polytrauma care *(see box below)*.

Four levels of polytrauma care

VA's nationwide polytrauma system includes four levels of care:

• **Level 1**—These are VA's four main polytrauma centers, located in Tampa, Richmond, Minneapolis and Palo Alto. A fifth is planned for San Antonio. These sites provide comprehensive acute care and rehabilitation for veterans with the most severe wounds, many of whom arrive straight from military hospitals such as Walter Reed Army Medical Center.

• **Level 2**—These sites service veterans who need somewhat less intensive care. Care teams at these sites coordinate long-term rehabilitation services as needed. Each of VA's 21 nationwide Veterans Integrated Service Networks, or VISNs, has at least one Level 1 or Level 2 facility.

• **Level 3**—These facilities have teams with rehabilitation expertise that deliver follow-up services in consultation with regional and network specialists. By way of example, VISN 11, which spans 90,000 square miles in four Midwest states, has three Level 3 sites.

• **Level 4**—These sites have at least one person who handles consultation, assessment and referral of polytrauma patients to higher-level facilities.

Mapping maven—Diane Cowper Ripley, PhD, of VA's Rehabilitation Outcomes Research Center in Gainesville, Fla., received her first research grant from VA in 1987 to study the migration patterns of retired veterans. Most recently, she has used GIS—sophisticated geographic software—to track access to polytrauma care for seriously wounded veterans.

Among the findings: About 88 percent of the veterans in the database had "reasonable" access to VA's multi-tiered system of polytrauma care. The median driving distances to the top three levels of facilities—from comprehensive "Level 1" facilities to supportive "Level 3" sites—were 411, 121 and 64 miles, respectively.

Other findings:

• Hearing impairment was the most common traumatic injury, affecting some 63 percent of the veterans, followed by vision loss, orthopedic injuries, traumatic brain injury (4.2 percent), burns, spinal cord injury, and amputation (1.3 percent). Just over five percent of the veterans had polytrauma wounds—multiple, complex injuries requiring intensive therapy.

• Four counties in Alabama and one county in each of six states were identified as areas with potential gaps in access to rehabilitation care. The states were Nevada, North Dakota, Texas,

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Hawaii, Alaska, and Mississippi. Clark County, Nevada—the area around Las Vegas—and El Paso County, Texas, had the highest numbers of patients outside of what were considered reasonable drive time bands.

• For each mile a veteran was closer to a Level 2 polytrauma site, the odds of receiving rehabilitation services increased one percent.

The study yielded numerous other analyses relating to the places veterans live and the nearest VA rehabilitation services. Partly as a result of the data, VA is now moving to upgrade the polytrauma care available in San Juan, where, according to Cowper Ripley, a relatively large portion of the population serves in the military and a high percentage of veterans enroll in VA care.

Mapping software offers 'nice way to communicate across disciplines'

The software used by the Gainesville group is known generally as Geographic Information Systems, or GIS. It's used widely by planners in many fields—by retailers, for example, to know where to build new stores, and by police departments to track crime patterns. If you've ever used Web-based consumer programs like Mapquest or Google Maps, you have a rough initial sense of what GIS can do. Just imagine adding in lots of powerful analytical and statistical features and a huge palette of mapping and graphics tools.

Policymakers at VA headquarters who use the software rely on studies at the RORC and other research sites to support their efforts. "GIS is a nice way to communicate across disciplines and for researchers to communicate with policy people," says Cowper Ripley. "When you show the picture and point out what you've done, people can see what you're talking about. It's a lot better than presenting a statistical model."

The RORC researcher is quick to acknowledge that GIS-based research is only one of many factors that policymakers need to consider. But it makes their job infinitely easier, she says.

"This is a tool for policymakers so they can meet the needs of the largest numbers of patients. It helps them narrow down the possibilities and focus on key geographic areas." For instance, the software allows users to quickly play out different scenarios—adding a Level 2 or 3 facility in a particular location, for example, and seeing, in theory, how many additional veterans would be served.

Says Cowper Ripley, "I think GIS is really helpful to management for making that first cut, and that's what its real utility is."

Denise Herring is in a study at the Baltimore VA to determine how different types of exercise—including treadmill work—affect stroke recovery.

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aerobically fit at the end of the study, whereas aerobic capacity had declined slightly in the stretching group.

Moreover, the investigators took new brain scans and found increased activity in brain areas associated with walking among all the treadmill exercisers. Brain scans of patients in the stretching group showed no such changes. "This suggests that the brain is responsible for the improvement we saw in patients' walking ability. It seems to be recruiting other regions [of the brain] to take on the job of areas damaged by stroke," said Andreas Luft, MD, a visiting researcher from Germany who helped lead the study.

Those patients with the most improvement in walking showed the strongest change in brain activity, though the researchers don't yet know whether these brain changes were caused by more walking or whether participants walked better because brain activity in these key areas increased. This question will be the focus of future research.

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years after a stroke. Typically, stroke patients have been told to accept their disabilities as permanent, whereas survivors of heart attacks, for instance, are often put on exercise regimens to rebuild their strength and endurance. Most stroke rehabilitation programs focus on short-term recovery and end just a few months after the patient's stroke. As a result, improvements level off and fitness and mobility wane over time—which itself can raise the risk of a second stroke, diabetes or other diseases.

But experts are moving toward a new approach, thanks to research such as a recent treadmill study led by Macko *(see box on page two)*. According to George Wittenberg, MD, PhD, a neurologist at the Baltimore VA who is helping to lead a multisite VA clinical trial on robots in stroke rehabilitation, research has led to a new understanding of brain "plasticity"—the ability of the brain to form new neural pathways and "rewire" itself to restore lost function.

"The older thinking was that approximately a year after a stroke, there wasn't any useful neuroplasticity and that further therapy wouldn't have any further effects on motor function," says Wittenberg. "But there have now been several studies using a variety of techniques that have shown … that there is plasticity that goes on long after a stroke."

That's good news for people like 69-year-old veteran Earl Elsey Jr., who suffered a stroke in 2004. For the past six months, he's been using a treadmill three times per week at the Baltimore VA as part of a study on how different types of exercise—stretching, intense walking, or longer-duration walking—affect fitness, balance, walking ability, and everyday function. He says his fitness and balance are "80 percent better" and notes that he's been able to reduce his medication for both diabetes and high blood pressure. Most of all, he credits the education he's received through the study as a key factor in his motivation to keep on exercising. "Not only have I improved physically since coming here," says Elsey, "but I've learned about all the things I can do to deal with stroke. I've learned how to take care of myself."

Stroke studies span lab, clinic—Top photo: In the Molecular Pathology Lab at the Baltimore VA, Lara Wiley (left) and Guoyan Li prepare to do a "microarray" to analyze the proteins in muscle tissue biopsied from a stroke patient. Bottom photo: Delores Royster, newly enrolled in a stroke study, receives a physical exam from nurse practitioner Laura Mastella.

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substantially to help fill these gaps," said Stein. "We will bring together psychologists, psychiatrists, neurologists, neurosurgeons, trauma surgeons and rehabilitation specialists at academic research centers, VA hospitals and active military sites nationwide to help us understand what happens to people who suffer traumatic injuries, including mild head injuries such as concussions. This will help us design treatments that can most appropriately address the needs of people who develop PTSD and TBI—and, hopefully, even find ways to prevent them."

Stein, who is also funded by VA to study the neurobiology of PTSD in women, noted that an area of particular focus for the new consortium will be the poorly understood link between PTSD and TBI. The two conditions can overlap and mesh in complex ways, making accurate diagnosis and effective treatment more difficult. "Both PTSD and TBI frequently occur in the same patient after an injury," said Stein. "The [consortium] will be devoting special efforts to understand and develop treatments for the overlap between these two conditions."

INVESTIGATOR SNAPSHOT

Cancer gene hunter—Sushanta Banerjee, PhD, founding director of the Cancer Research Unit at the Kansas City (Mo.) VA Medical Center, has been studying cancer for two decades. His group was the first to describe the role of a gene called CCN5 in human breast and pancreatic cancer. He calls the gene "anti-invasive" in that it appears to stop tumors from spreading. His quest now is to develop ways to "turn on" CCN5 in cancer cells in which the gene has become inactive and to learn which genes become activated—and promote metastasis—when CCN5 is turned off.

"Cancer is a mixed bag of cells that use a lot of different tactics to survive," says Banerjee. "That's why we are not focusing only on one gene, but on multiple genes, and why we need to know this disease in-depth. We know a lot more about breast cancer, for example, than we did 10 years ago, and as a result we are developing many new drugs. In the next 10 years, we can further expand the therapies that are available."