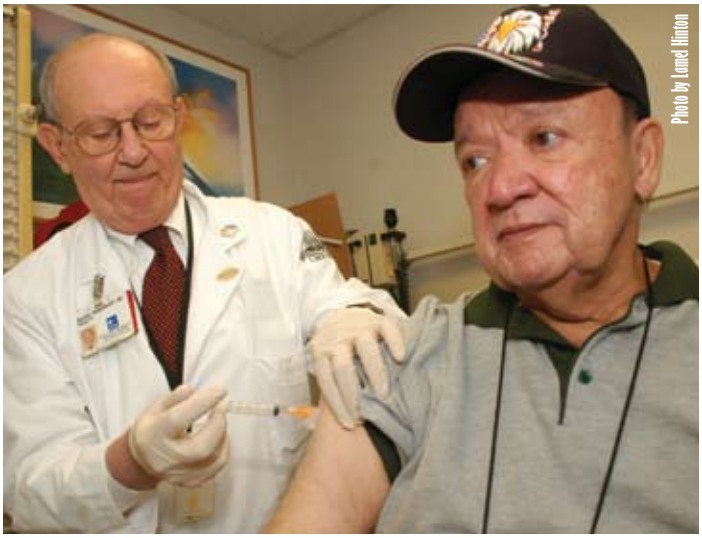
JUNE 2010

VA Research Currents

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



Dr. Michael Simberkoff administers the shingles vaccine to Veteran Marco Antonio at the VA New York Harbor Healthcare System.

Shingles vaccine safe but not widely used

A vaccine to prevent shingles—a painful nerve and skin infection that mainly affects older adults—is safe over the long term, according to a report in the May 4 *Annals of Internal Medicine.* The findings are based on data from a nationwide study conducted by VA and the National Institutes of Health from 1998 to 2004. However, other research shows the vaccine, made by Merck and sold as Zostavax, is not yet being used widely in VA or by U.S. health care providers in general.

In 2005, VA and NIH researchers reported in the *New England Journal of Medicine* that the vaccine cut the incidence of shingles, also known as herpes zoster, by more than 50 percent and dramatically limited its severity and complications. The vaccine was well-tolerated in the trial, with the most common adverse side effect being short-term swelling or irritation at the injection site.

The new *Annals* report is based on an additional three years of follow-up on the nearly 39,000 men and women who took part in the trial. The researchers also collected more extensive

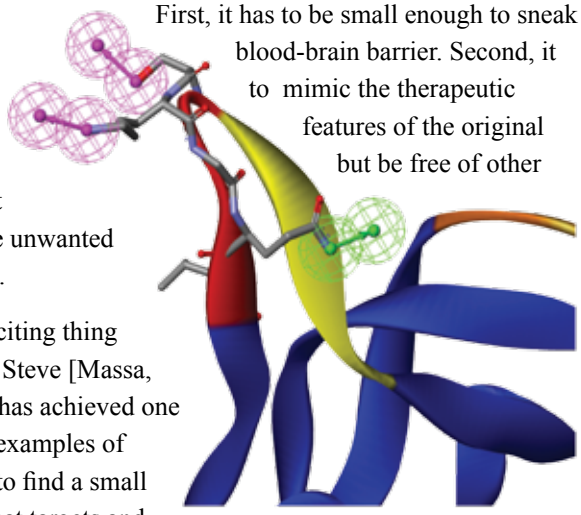
see **SHINGLES** on pg. 4

The smaller the better: Seeking new drugs that can reach the brain

The illustration is almost cartoonlike: Its curvy, colorful stick figures resemble two dancers doing a dip.

But the image, which represents part of a protein molecule, was part of an article in a respected medical journal and reflects a knowledge breakthrough that could speed the path to new drugs to treat brain disorders.

The report in last month's *Journal of Clinical Investigation,* by VA researchers and colleagues, shows how computer modeling can be used to zero in on small, key pieces of proteins and then scour huge libraries of compounds for small molecules with similar properties. The idea is to find a new molecule with two traits: First, it has to be small enough to sneak through the blood-brain barrier. Second, it has to mimic the therapeutic chemical features of the original protein but be free of other aspects that could cause unwanted side effects.



"The exciting thing here is that Steve [Massa, MD, PhD] has achieved one of the first examples of being able to find a small molecule that targets and activates a receptor normally targeted by a protein. It has huge implications for drug development," says Frank Longo, MD, PhD, who collaborated with Massa on the study.

Massa directs the Laboratory for Computational Neurochemistry and Drug Discovery at the San Francisco VA Medical Center and the University of California, San Francisco. Longo, his longtime collaborator, was formerly with VA and is now chair of neurology at Stanford University.

The team's latest discovery is a group of molecules that mimic a protein known as BDNF—short for brain-derived neurotrophic

see **DRUGS** on pg. 3

Trial provides insight on Parkinson's treatment

Two target sites for 'deep brain stimulation' both prove effective

Study results from VA and the National Institutes of Health show that deep brain stimulation (DBS)—a surgical treatment that dramatically improves movement-related symptoms for many patients with Parkinson's disease—works equally well at either of two sites in the brain. The findings appeared June 3 in the *New England Journal of Medicine.*

The new findings are the latest from a major study initially published last year in the *Journal of the American Medical Association.* The trial, conducted at seven VA sites and six university hospitals, found that DBS is somewhat riskier than carefully managed drug therapy but may offer significant improvement for those with advanced Parkinson's who no longer respond well to medication alone. Most DBS patients in the study were able to reduce their medication substantially.

The new report is based on a two-year comparison of outcomes in 299 patients who underwent DBS. It shows that stimulation of either of the two brain regions normally targeted in DBS can effectively control motor symptoms and boost quality of life.

Photo by Jules Visotto

Veteran George Schmid, a patient at the Philadelphia VA Medical Center, had two brain electrodes and a pacemaker-like device implanted in 2006 to treat his Parkinson's disease.

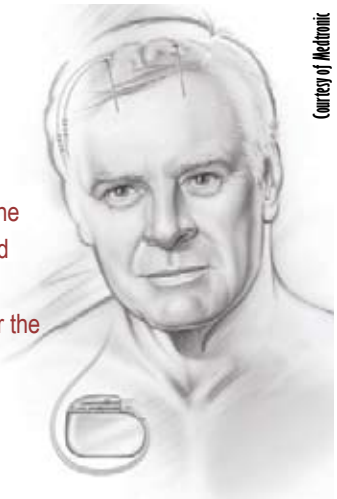
In DBS, surgeons implant electrodes in the brain and run thin wires under the skin to a pacemaker-like device placed under the skin near the collarbone. Electrical stimulation from the battery-operated device jams the brain signals that cause motor symptoms such as stiffness and tremors. Thousands of Americans have had DBS since it was introduced a few years ago, and many have reported major improvements. But questions have remained about which stimulation site in the brain yields better outcomes.

Earlier studies suggested that better motor control could be achieved by stimulating the subthalamic nucleus (STN) rather than the globus pallidus interna (GPi)—two areas of the brain involved in movement. On the other hand, GPi stimulation was found to possibly pose less risk of side effects such as depression or impaired thinking.

The new VA-NIH analysis finds both sites roughly equal for motor outcomes. There were subtle differences between the sites in terms of cognitive skills and mood—mainly in line with past research findings—but the full clinical significance of the differences is not yet clear.

Serious adverse events occurred equally across both groups. The most common problem was surgical-site infection, occurring in fewer than 10 percent of

see **STIMULATION** on page 6



Courtesy of Medtronic

In deep brain stimulation, electrodes are implanted on both sides of the brain and wired to a stimulator implanted near the collarbone.

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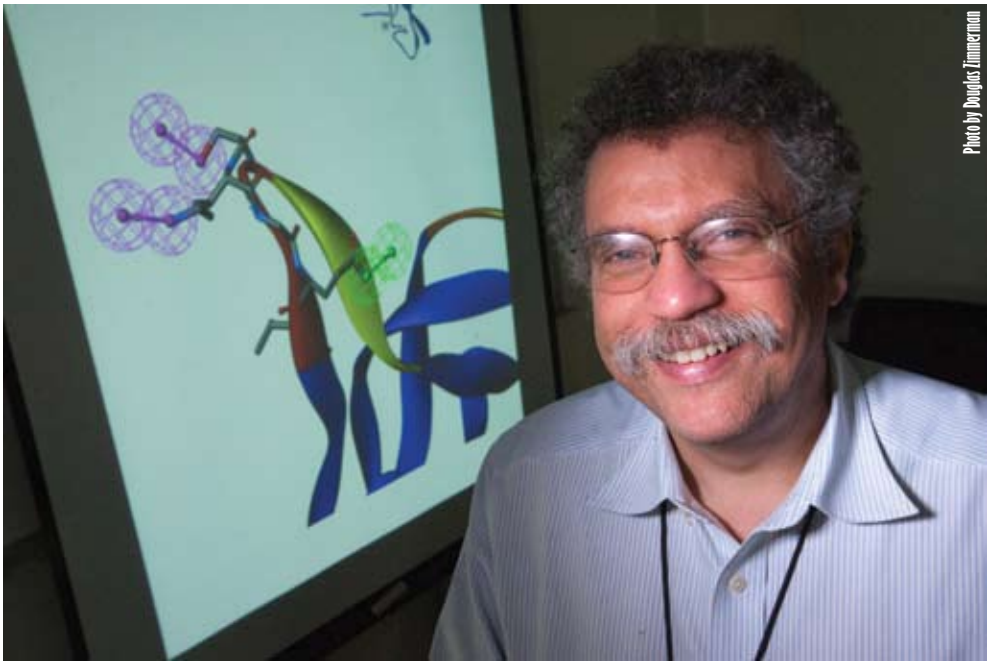


The art and science of drug discovery— Dr. Stephen Massa's lab creates virtual 3D models of proteins to study their structure and chemical features and to search for related compounds that might have therapeutic value for brain disorders.

DRUGS *(from page 1)*

factor. As the name suggests, this naturally occurring brain chemical helps neurons grow and has shown promise, at least in animal studies, for treating conditions ranging from traumatic brain injury to depression to Alzheimer's disease.

"It has so many potential therapeutic applications that [developing BDNF into a drug] has been a dream in academia and the pharmaceutical industry," says Longo. "People overuse the term 'holy grail,' but I think it applies in this situation."

The problem, though, is how to get BDNF to the brain. Giving it orally or injecting it intravenously doesn't work well because of its poor ability to cross the blood-brain barrier. As a result, some researchers have tried injecting it directly to the brain. That approach would likely be too risky in humans. Other studies have used virus- and cell-based techniques to increase BDNF in the brain. These methods, too, are fraught with medical risk. Another problem with BDNF is that while it appears to help the brain, it can also cause pain and other unwanted side effects.

'The idea is to take a piece of a much larger protein ... and use it as a probe. ...'

Longo has pioneered the approach of whittling down brain-boosting neurotrophic proteins to find the smallest possible region that packs the desired therapeutic punch. Massa's lab creates virtual 3D models of proteins and uses them to study the proteins and seek similar molecules that might work better as drugs. Massa explains how his work and Longo's merge: "The idea is to take a piece of a much larger protein—a piece that binds to a specific receptor—and to use it as a probe for finding new molecules with the desired therapeutic properties."

In their search for a molecule to mimic BDNF, Massa and Longo, along with collaborator Tao Yang, PhD, and other colleagues, hit on a family of compounds called LM22A. Their recent article reports on experiments in which one of the molecules, LM22A-4, worked as well as BDNF to improve the survival of mouse neurons in culture. In work performed in Massa's VA lab by Jian Shi, PhD, the compound also improved learning in rats with traumatic brain injury.

However, the discovery is not yet quite the "holy grail" Longo refers to, as LM22A-4 doesn't cross the blood-brain barrier as well as the researchers would like. But their latest work, taken together with a similar finding they reported in 2006, is further proof that software-based methods can pinpoint hot candidate molecules, even among the millions of compounds available nowadays through the libraries of biochemical manufacturing labs.

Massa and Longo say they will go on seeking other small molecules that can mimic BDNF, but they also aren't done exploring the LM22As, which until now have had scant if any mention in the scientific literature. "The potential actions of these compounds are broad," notes Massa, "and there's a lot more to learn about how they work and what they might be applied to."

Picturing proteins

The software that researchers use nowadays to create colorful, 3D models of proteins incorporates information derived from X-ray crystallography. In this lab technique, proteins are condensed into a solid crystal. X-rays directed at the crystal produce a distinctive set of reflections. The pattern helps scientists reconstruct the physical structure of the protein.

SHINGLES *(from page 1)*

details on possible side effects from a subgroup of more than 6,000 patients.

According to lead author Michael Simberkoff, MD, of the VA New York Harbor Healthcare System, the new analysis "confirms and expands the safety profile of the herpes zoster vaccine that was originally reported in 2005."

The study found that serious adverse events, such as hospitalizations, occurred in only 1.4 percent of participants, and were no more common in the vaccine group than in those who received a placebo injection. Minor side effects such as swelling and redness were more common in the vaccine group (48 percent) than in the placebo group (16 percent), and were more common in people in their 60s than in participants who were older than 70. (Everyone in the trial was over age 60.)

Shingles rates rising despite availability of vaccine

Despite the vaccine's reported efficacy and safety, though, it is not yet being widely used, either in VA or elsewhere. Fewer than 10 percent of eligible U.S. adults are getting the vaccine, according to published reports.

Moreover, a recent study appearing in *Clinical Infectious Diseases* found an increasing incidence of shingles among Veterans: about five cases of shingles per 1,000 VA patients in 2007, versus about three episodes per 1,000 patients in 2000. David Rimland, MD, chief of infectious diseases at the Atlanta VA Medical Center and lead author on the study, says the incidence has since risen to about six cases per 1,000 Veterans in 2009.

Additional efforts in works to promote vaccine

Both Rimland and Simberkoff say the vaccine could help stem the trend if it were promoted more effectively to patients and physicians. "The herpes zoster vaccine is not being used as widely as it could or should be," in or outside VA, says Simberkoff. "We must improve education about this and other adult vaccines in the medical profession and among consumers—the older patient population."

A study that appeared along with Simberkoff's article in the May 4 *Annals of Internal Medicine* found that outside VA, barriers to the vaccine's use include issues

see **SHINGLES** on pg. 8

Shingles can mean anguishing long-term pain

Shingles, also known as herpes zoster, is caused by a re-awakening of dormant chickenpox virus in the body. It is marked by a painful, blistering rash. It can affect anyone who had chickenpox as a youth—virtually all middle-aged and older Americans—and half of those who live to 85 will get the disease. Doctors in the United States treat about a million cases each year. Most cases clear up within a week, but some patients suffer anguishing nerve pain for years. While not life-threatening, this complication can bring on insomnia, weight loss, depression and other medical problems.

"For some people, shingles can ruin their retirement and their lives," said Michael Oxman, MD, an infectious disease specialist at the San Diego VA Healthcare System who led the original VA-NIH vaccine study. "If the side of your body is affected, just the touch of a shirt is painful. If you have it on your head, even a breeze can be intolerably painful."

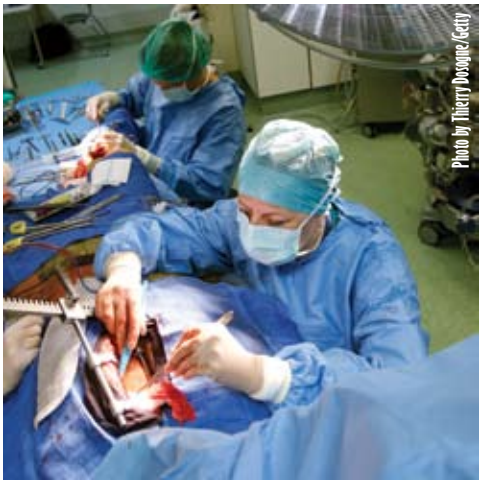


Photo by Thierry Dosogne/Getty

For patients recovering from surgery, pneumonia is the third most common complication.

Pilot program cuts post-surgery pneumonia

A pilot program at the VA Palo Alto Health Care System showed that a set of relatively easy steps could dramatically reduce the number of patients who contract pneumonia after surgery. Results of the study were reported in April in the *Journal of the American College of Surgeons.*

In the U.S., pneumonia is the third most common post-surgery complication, after urinary-tract and wound infections. It can result in tens of thousands of dollars in extra costs per patient and is often fatal.

Among the interventions in the VA study: extra training and care-documentation requirements for nurses; computerized reminders for doctors; special breathing exercises for patients; twice-daily oral swabs with chlorhexidine; and measures designed to improve patients' head elevation during meals and sleep.

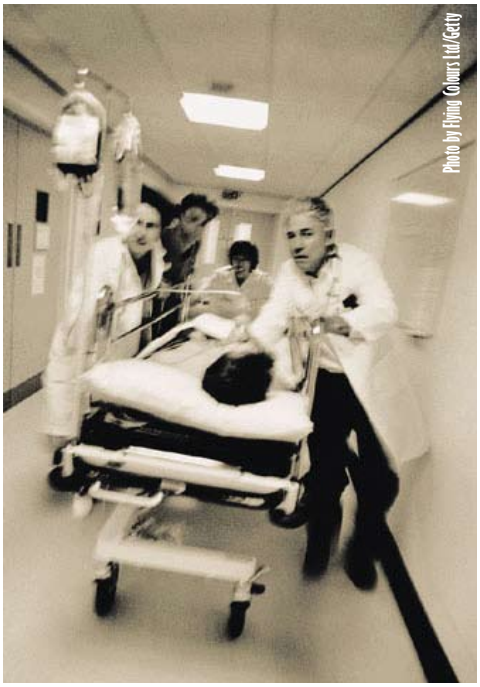
"Our research shows that simple steps in prevention can have a substantial effect," said Sherry Wren, MD, chief of general surgery at the Palo Alto VA and a professor of surgery at Stanford University. She said the program, if expanded to other VA or private hospitals, could help improve patient outcomes and survival and reduce costs.

New saliva test may help diagnose heart attack

A diagnostic tool to detect heart attacks using a person's saliva is being tested at the Michael E. DeBakey VA Medical Center in Houston through a partnership with neighboring Baylor College of Medicine and Rice University's BioScience Research Collaborative.

"The device works by analyzing saliva, looking for cardiac biomarkers of injury implicated in the heart attack," said Biykem Bozkurt, MD, chief of cardiology at the Houston VA and a professor at Baylor.

The device, called the Nano-Bio-Chip, was developed by Rice bioengineer John McDevitt, PhD. Winner of a 2008 *Popular Science* "Best of What's New Award" and inventor of a "lab-on-a-chip" system to diagnose oral cancer, McDevitt said he envisions Houston as the hub of a "biomarker highway" where the biochip will be configured to diagnose a variety of diseases.



Each year, more than a million Americans suffer heart attacks, about half of them fatal.

Is it a heart attack?—Dr. Biykem Bozkurt is leading a clinical trial at the Houston VA Medical Center to test a biochip that rapidly detects biomarkers in saliva that have been linked to heart attack.

Chest pain brings about five million people to U.S. emergency rooms each year, but 80 percent of them are not suffering heart attacks. Electrocardiograms are often inconclusive, and blood tests that look for biomarkers can take several hours.

With the Nano-Bio-Chip, a patient's gums are swabbed with a cotton-tipped stick and the saliva is transferred to the disposable microchip. The chip is then inserted into an analyzer and within a few minutes, the saliva sample is checked for results.

"We find the electrocardiograms provide more accurate information when combined with the saliva test," McDevitt said. "Saliva-based tests have the potential to quickly diagnose heart-attack victims as well as to find false alarms."

Over the next two years, some 500 ER patients at the Houston VA are expected to take part in the study. They'll provide both blood and saliva samples, and the two diagnostic methods will be compared.

"It is anticipated that saliva will be an alternative or complementary technique to blood drawing for early diagnosis of heart attacks, ultimately for testing in the ambulance before arrival in the emergency room," said Bozkurt.

Genetic probe for heart-transplant rejection

Patients who have had cardiac transplants typically undergo heart-tissue biopsies during the first few years after the transplant to check for signs of organ rejection. Now, a team with VA and Stanford University has shown that a test that requires only a blood sample may work just as well to monitor low-risk patients, and would require less risk and discomfort for patients. The test, known as AlloMap, scans blood cells for RNA produced by about a dozen genes shown in prior research to help distinguish between rejection and non-rejection. Results from the study of 602 cardiac-transplant patients, which was sponsored by the company that makes AlloMap, appeared May 20 in the *New England Journal of Medicine.*

CAREER MILESTONES

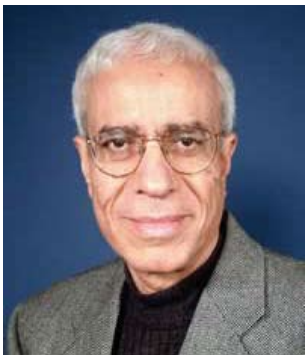
Stephen Fausti, PhD, received the American Academy of Audiology's 2010 James Jerger Career Award for Research, the group's highest honor. Fausti, founder and director of VA's National Center for Auditory Rehabilitative Research, is credited with spearheading the development of new equipment, diagnostic tests and clinical strategies to help Veterans and others with hearing loss, tinnitus and vestibular disorders. Among his innovations are custom instrumentation and new techniques for obtaining electrophysiological measures of high-frequency auditory function. These developments are especially useful for patients who cannot respond reliably to behavioral tests because of age, injury, illness or other factors.


Fausti

Suzana Iveljic, MBA, director of operations and external relations for VA's Advanced Platform Technology (APT) Center, was recognized as a "Patriotic Employer" by the National Committee for Employer Support of the Guard and Reserve. She was nominated by an employee of the center for her efforts to support his military reserve commitments. The APT Center, one of a network of VA rehabilitation research centers of excellence across the nation, is based at the Cleveland VA Medical Center.


Iveljic

Nabil El-Sherif, MD, received the 2010 Pioneer in Cardiac Pacing and Electrophysiology Award from the Heart Rhythm Society. El-Sherif, director of cardiology at the Brooklyn campus of the New York Harbor VA Health Care System, studies the biological basis of abnormal heartbeats. Among other contributions to the field as a researcher and mentor, El-Sherif pinpointed the electrical circuitry within the heart that should be targeted to stop the impulses that cause the rapid heartbeat seen in atrial flutter. His work enabled the successful clinical use of catheter radiofrequency ablation to treat the condition.


El-Sherif

Chester Ho, MD, chief of spinal cord injury at the Louis Stokes Cleveland VA Medical Center, received *Crain's Business Magazine's* Healthcare Hero 2010 Award (Physician's Category) for his groundbreaking work in the treatment of pressure ulcers. Pressure ulcers, or bed sores, are one of the most serious yet preventable afflictions affecting patients with spinal cord injuries. Ho developed an innovative treatment called pulsatile lavage—a procedure used to clean wounds. It has become the standard of care for pressure ulcers in the Cleveland VA's spinal cord injury unit. Ho is also an investigator at the Functional Electrical Stimulation Center, based at the Cleveland VA, where he is studying the use of electrical stimulation to treat pressure ulcers.


Ho

STIMULATION *(from page 2)*

patients in both groups. Almost all the adverse events were resolved over the two-year study period. One surgery-related death was reported, stemming from a brain hemorrhage.

Lead author Kenneth Follett, MD, PhD, of the Iowa City VA Medical Center said that overall, "Physicians and patients can have confidence in both types of DBS" as being effective for motor improvement. He said doctors should also consider the subtle differences that emerged in the comparison in other areas—for example, mood, cognition, or medication use—when making DBS treatment decisions with patients. The best candidates for the procedure, he said, are patients who have ongoing problems with movement despite medication or who suffer troubling side effects from the drugs, and who do not have significant cognitive problems or contraindications to surgery.

Patients who took part in the VA-NIH trial will be followed for several more years so researchers can further tease out the relative benefits of each DBS approach.

The study was sponsored by VA's Cooperative Studies Program and the National Institute of Neurological Disorders and Stroke, part of NIH.

About Parkinson's

Parkinson's disease, a progressive neurological disorder, affects some 1.5 million Americans, with 50,000 new cases diagnosed annually. VA treats at least 40,000 Veterans with the disorder each year. Most patients are over age 50, but some forms of the disease can strike younger adults.

Symptoms include slow movement, poor balance, shaking and muscle stiffness. Other signs may be a stiff facial expression, shuffling walk, muffled speech and depression. Symptoms may worsen over time. The disease is caused by a loss of brain cells that make dopamine, a brain chemical that helps control movement, emotion and other functions. For the past 30 years, treatment has centered on levodopa, a drug that is converted to dopamine in the brain.

Shaping the future of women's care in VA

Experts gathering in July to identify pressing health issues and forge research agenda

An upcoming meeting focused on health care for women Veterans is expected to play a key role in shaping VA's research agenda in this area over the coming years.

The National Meeting on Building the Evidence Base to Improve Health Care and Outcomes for Women Veterans will take place July 15 – 16 in Washington, DC. The meeting is the first event of its type since 2004, when VA first set out to develop a comprehensive research agenda focused on women. Women now account for 14 percent of active duty military and nearly 6 percent of VA health care users.

"This year's meeting is an opportunity to gauge how far we have come since the establishment of the research agenda and to accelerate our growth towards research that will directly impact the care that women receive in VA," says Elizabeth Yano, PhD, MSPH. Yano is co-director of VA's Center for the Study of Healthcare Provider Behavior and an adjunct professor of health services at the University of California, Los Angeles, School of Public Health.

She said the July conference will "partner senior VA leaders with researchers in the field" to explore how to best use research to guide care and services for women. Leaders from several VA offices, such as the Center for Women Veterans, are expected to attend, as are researchers and women's health experts from the military, other federal agencies, and the nonprofit and private sectors.

At the meeting, dozens of VA researchers will present study results on access to care and quality of care for women Veterans; interventions to improve care and outcomes; post-deployment mental health care for women; the overall effects of military service on women's health; and steps to transform VA care for women. In the last few years, VA has funded a diverse portfolio of research for women Veterans that has resulted in more than 75 journal articles per year.

Examples of current VA studies focusing on women's health include a $5.6-million study of Vietnam-era women Veterans, and a comprehensive national survey of women Veterans, the first since 1985. More than 3,600 women are taking part in that effort.

Also, a synthesis of published research on women Veterans from the past five years is being completed by VA researchers in time for the July meeting and will help guide efforts to improve VA care for this fast-growing segment of the Veteran population.

Photos: (From left) U.S. Air Force Capt. Dana Arrieta manages the radar aboard an E-8 Joint Surveillance Target Attack Radar System aircraft; U.S. Air Force Academy Cadet 1st Class Morgan Trevarthen motivates a fourth class cadet during Recognition events at the academy; U.S. Air Force 1st Lt. Erica McCaslin, an 816th Expeditionary Airlift Squadron pilot, pushes a pallet onto a C-17 Globemaster III aircraft.

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Inside: **Large VA-NIH trial yields new insights on Parkinson's treatment**

SHINGLES *(from page 4)*

relating to cost and reimbursement, and lack of knowledge about the vaccine on the part of physicians.

Rimland confirmed that while cost is generally not an issue for VA patients, storage of the vaccine—it has to be kept frozen—can be an obstacle at smaller VA clinics not equipped with freezers. He says that in his region, a group is working to address the issue. He adds that across VA, "There has not been an aggressive push for the vaccine as we have had for the influenza vaccine."

Linda Kinsinger, MD, MPH, chief consultant for preventive medicine for VA and director of the agency's National Center for Health Promotion and Disease Prevention, noted that the vaccine is covered in a set of "Guidance Statements" that her program is preparing to issue for VA clinicians.

The guidance will be consistent with that of the Advisory Committee on Immunization Practices, a body appointed by the Department of Health and Human Services, and will include links to staff and patient-education tools. Says Kinsinger, "We hope that this guidance will increase the uptake of [the shingles vaccine] within VA facilities."

U.S. Army soldiers with 2nd Battalion, 12th Infantry Regiment, Task Force Lethal, prepare to move from cover during an attack by anti-Afghan forces in Kunar province, Afghanistan, in March 2010.

Study finds range of readjustment problems

Based on survey responses from 754 combat Veterans of the wars in Iraq and Afghanistan who use VA health care, a team at the Minneapolis VA Medical Center reported that from 25 to 56 percent had at least some difficulty in areas such as social functioning, productivity and community involvement.

At least a third of the Veterans in the nationwide sample reported divorce, dangerous driving, increased alcohol or drug use, or anger problems since deployment. Almost all expressed interest in services to help them readjust to civilian life, and many indicated they'd like to receive services via the Internet. About 40 percent screened positive for posttraumatic stress disorder, and probable PTSD was associated with reporting more readjustment difficulties and expressing interest in more types of services, including traditional mental health services.

The findings appeared in the June 2010 issue of the journal *Psychiatric Services.*