

Researchers seek efficient strategy to cope with drug-resistant germ

If the TV show “America’s Most Wanted” were to switch its focus from criminals to bacteria, the first episode would likely feature “methicillin-resistant *Staphylococcus aureus*,” or MRSA.

The tough-to-treat germ has long been the nemesis of infection-control experts in hospitals. But recent reports have produced alarming new data and suggested the problem is bigger than previously thought: MRSA is escaping the confines of hospitals, spreading in communities, and causing more than 94,000 serious infections and nearly 19,000 deaths each year. If the estimates are accurate, MRSA is killing more Americans than HIV/AIDS or homicide.

VA hospitals have been in the forefront of learning how to deal with the tenacious bug. Based on a successful pilot study at the VA Pittsburgh Healthcare System that cut infection rates by 50 percent, VA nationwide began screening all incoming patients on its intensive care units in March 2007 with a nasal swab and MRSA culture. Those found to be carrying the bug are isolated to prevent it from spreading. Anyone entering the patient’s room must wear

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Eli Perencevich, MD, a physician-investigator at the Baltimore VAMC, administers a nasal swab to newly admitted patient Louis Romm to test for MRSA.



Patients in VA polytrauma care, such as this veteran at the Tampa VA Medical Center, may benefit from a research project aimed at training peer visitors.

Peer-visitor project fosters mutual help among veterans with polytrauma

Rehabilitation psychologist Rhonda Williams, PhD, of the Puget Sound VA says that among the veterans she’s worked with, “There’s very much a help-your-buddy mentality.” She and her colleagues are capitalizing on that mindset as they look to develop training materials for a polytrauma “peer visitation” program.

The effort, funded by VA’s Health Services Research and Development Service, is modeled after a program developed by the

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Blood test may offer early detection for Alzheimer's disease

Researchers have identified a set of proteins in the blood that appear to predict the onset of Alzheimer's disease and could be the basis of a screening test. The findings are reported in the current issue of *Nature Medicine* by an international team led by Tony Wyss-Coray, PhD, of the VA Palo Alto Healthcare System and Stanford University.

The team initially analyzed hundreds of archived blood samples from the U.S., Sweden, Poland and Italy, taken from people whose conditions ranged from normal to advanced Alzheimer's. The researchers compared the levels of 120 "signaling" proteins—molecules that enable communication between cells—and looked for a pattern unique to Alzheimer's. Their quest for an Alzheimer's-specific "signature" identified 18 proteins whose concentrations varied in specific ways only in the disease samples.

When Wyss-Coray's team tested the biomarkers with an additional 92 blood samples, the protein analysis matched the clinical diagnosis about 90 percent of the time. Even more intriguing was the next phase of the experiment: Used on blood samples from 47 people with mild cognitive impairment—an Alzheimer's precursor—the test predicted with about 80-percent accuracy which patients would



Tony Wyss-Coray, PhD.

develop Alzheimer's two to six years after the samples had been taken.

Researchers have tried other methods of predicting Alzheimer's disease—for example, by measuring other markers in the blood or urine, or using various brain-imaging techniques—but so far no single test has proved reliable and practical. To diagnose the disease, doctors use an array of medical and neuropsychological tests. But the only definitive diagnosis is through autopsy after a person has died, when the brain plaques and tangles that mark the disease can be clearly seen.

While no treatments are yet available that can halt Alzheimer's or dramatically improve symptoms, the Alzheimer's Association says early detection is valuable for a variety of reasons, such as the opportunity to plan appropriate care or seek out experimental treatments.

"If I had memory problems, I would want to know if it were Alzheimer's or

Researchers have identified 18 proteins in the blood that could be the basis of a screening test for Alzheimer's.

something else, and probably enroll in some of the ongoing clinical trials. I would also take currently available medications—they are no cure but seem to have significant benefits overall to patients," said Wyss-Coray, who is an investigator with the Geriatric Research, Education and Clinical Center at the Palo Alto VA and associate professor of neurology at Stanford.

The scientist, who is funded by VA to study the role of the immune system in Alzheimer's disease, says the 18 proteins that appear to signal the disorder are involved with various immune functions, as well as the production of new blood cells and the disintegration of cells that are no longer needed.

"Our hypothesis is that there is something wrong with the production of certain blood cells, which may be needed to clear the stuff that accumulates in the brain in Alzheimer's disease," he said. "That makes a lot of sense, and it is very exciting to think of immune cells and molecules interacting with the brain."

Even though the new screening measure must undergo further study and validation, it has stirred considerable interest in the scientific community. Markus Britschgi, PhD, a postdoctoral fellow in Wyss-Coray's lab, said some colleagues have already expressed eagerness to reap benefit from the test for their own families. "Already we have people approaching us at meetings asking if they can give us a vial of their grandfather's blood for testing." ■

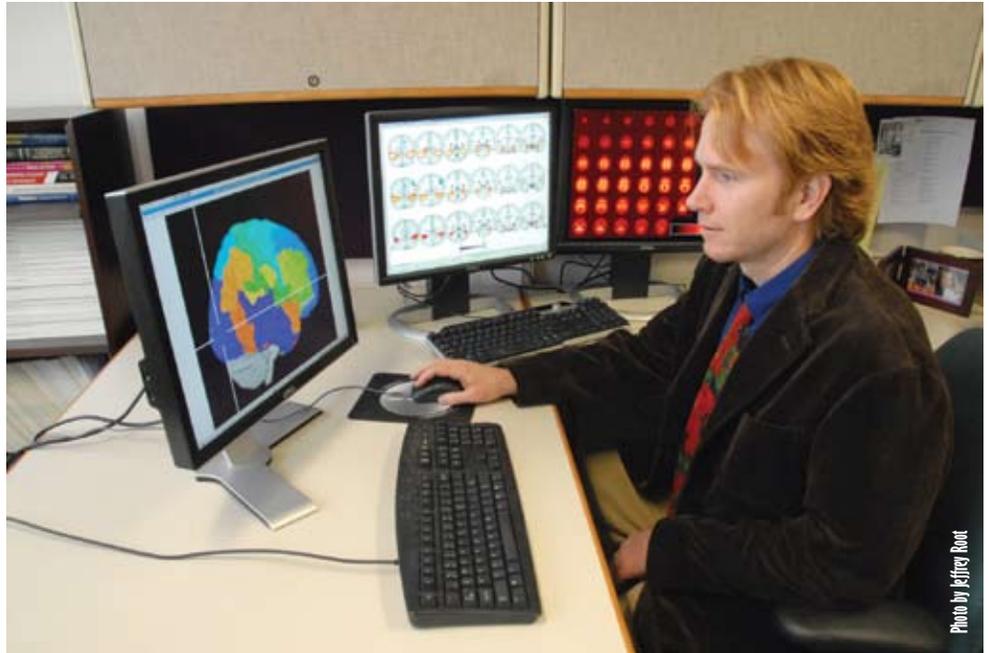
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Career milestones

Alfredo J. Selim, MD, a physician-investigator at the Center for Health Quality, Outcomes and Economic Research at the Bedford (Mass.) VA Medical Center, won the Peter Reizenstein Prize from the International Society for Quality in Health Care for the best paper published in the *International Journal for Quality in Health Care* in 2006. The paper was titled “Use of Risk-Adjusted Change in Health Status to Assess the Performance of Integrated Service Networks in the Veterans Health Administration.”

David Wofsy, MD, a staff physician and researcher at the San Francisco VA, received the 2007 Lee C. Howley Prize for Arthritis Research from the Arthritis Foundation. The award recognizes researchers whose contributions over the past five years have led to significant advances in the understanding, treatment or prevention of arthritis and rheumatic diseases. Wofsy’s research is devoted to the development of new therapies for autoimmune diseases, particularly systemic lupus erythematosus.

David Asch, MD, MBA, co-director of VA’s Pennsylvania-based Center for Health Equity Research and Promotion, is one of 65 newly named members to the Institute of Medicine—the medical arm of the National Academy of Sciences. Asch studies clinician and patient decision-making, medical ethics, and health disparities. Examples of his recent work include a study published in the *American Heart Journal* examining whether racial variations exist in the use of cardiac procedures throughout VA; and research published in the *International Journal for Quality in Health Care* focused on how health literacy affects patients’ satisfaction with their care.



Sterling C. Johnson, PhD, studies brain disorders that affect memory and self-awareness.

VA scientists receive presidential awards

VA researchers Sterling C. Johnson, PhD, and William S. Yancy Jr., MD, along with 56 scientists from eight other federal agencies, received Presidential Early Career Awards for Scientists and Engineers at the White House on Nov 1.

The annual awards, established in 1996 by the National Science and Technology Council, recognize top young scientists and engineers for their “innovative research at the frontiers of science and technology” and for their scientific leadership and community outreach.

Johnson is a clinical psychologist and neuroscience researcher at the William S. Middleton Memorial Veterans Hospital in Madison, Wis., and an assistant professor at the University of Wisconsin School of Medicine and Public Health. He uses brain imaging and neuropsychological measurement to study disorders that affect memory and self-awareness. One of his current VA-funded studies involves combat veterans with traumatic brain injury. His lab is using diffusion tensor imaging and

functional MRI to learn which areas of the brain are linked to the veterans’ awareness of their own cognitive, emotional and social deficits. Such awareness plays a critical role in recovery and adjustment.

Other studies by Johnson and colleagues focus on how early in life Alzheimer’s disease begins, and whether brain imaging can provide new knowledge about disease progression. His group at the Madison VA’s Geriatric Research Education and Clinical Center published a study in the Oct. 2007 *Archives of General Psychiatry* that found subtle abnormalities in the brain function of normal middle-aged adults whose parents had Alzheimer’s disease.

Yancy, a physician at the Durham VA Medical Center and an investigator at that site’s Center for Health Services Research in Primary Care, studies the effects of diet and exercise on obesity and its complications. A study by his group made headlines in 2004 when it showed that people on a

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gloves and a gown. In the past few months, the surveillance program has been expanded to hospital units besides ICUs.

Screening every patient, however, can be costly. Cultures run about \$10 each. That's why a research team at the Baltimore VA Medical Center is working on a more cost-effective solution.

"We're trying to figure out, do we really need to swab everyone, or can we determine the really high-risk people and only swab them," says physician-investigator Eli Perencevich, MD, MS.

He points out that clinical guidelines call for screening "high-risk" patients—but no one has a firm definition of who is "high risk." In a study that was conducted at the University of Maryland Medical Center—the Baltimore VA's academic affiliate—and published last year, Perencevich and colleagues swabbed 700 patients and probed their health histories. "It turned out that for MRSA, if you just asked them whether they had been admitted to the hospital in the past year, you could detect almost 80 percent of the people" carrying the bacteria, he says. That's because until recently, MRSA had largely been a hospital-acquired germ.

Down the street at the Baltimore VA, Perencevich's team is now administering a wider set of questions to newly admitted patients and culling data, when available, from their extensive VA electronic health records.

"What's nice about the VA data is that we're looking not just at hospital antibiotic exposure, but outpatient antibiotic exposure as well," he says. "Total antibiotic exposure is an important variable we're examining carefully. We want to know whether people who have had more antibiotic exposure are at higher risk for MRSA, and whether certain antibiotics put them at higher risk than others.

"We're trying to take the known risk factors for MRSA and determine which ones have the best predictive value. If we can determine 80 to 90 percent of who has MRSA by asking two questions, and therefore have to swab only 40 or 50 percent of admissions instead of 100 percent, we could save a lot of money."

Perencevich points out that such a streamlined approach could not only save money for VA, but bring huge benefits for private hospitals, which are not reimbursed for MRSA screening per se, and receive no financial reward for boosting quality by

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Methicillin-resistant Staphylococcus aureus (MRSA) at a glance

- Staphylococcus aureus is found in the nose and on the skin of about 3 in 10 healthy adults, and normally does no harm. But when infections do occur—often because of breaks in the skin—they can range from mild to fatal. Non-resistant strains of the bacteria can be treated with common antibiotics.

- According to 2005 data from the Centers for Disease Control and Prevention, MRSA infects nearly 32 in 100,000 people, with 58 percent of infections originating outside hospitals but in people with recent exposure to the healthcare system, and 27 percent originating in hospitals.

- It is estimated that MRSA now accounts for more than 60 percent of hospital staph infections, up from 2 percent in the mid-1970s.

VA research highlighted in House hearing

In a hearing on VA research held by the House Veterans' Affairs Health Subcommittee on Oct. 4, witnesses reviewed a number of research programs within VA and focused on three specific areas of need among returning service members: prosthetics, pain management, and vision.

Major Dave Rozelle of the Amputee Care Program at Walter Reed Army Medical Center testified that as of Sept. 2007, more than 700 service members in OIF/OEF had sustained a major limb amputation, and more than half of these men and women had also suffered a brain injury. He said these veterans' health challenges "require a unique approach to treatment and warrant dedicated research programs to optimize care."

Mark Lema, MD, PhD, representing the Pain Care Coalition, cited studies showing that more than 90 percent of those enrolled in VA polytrauma care have chronic pain, and that pain is the most common symptom in returning soldiers. He said advances in brain-imaging provide evidence that "unrelieved pain, regardless of its initial cause, can be an aggressive disease that damages the nervous system, causing permanent pathological changes in sensory neurons and in the tissues of the spinal cord and brain."

Thomas Zampieri, PhD, director of Government Relations for the Blinded Veterans Association, testified on the current need for vision research: "VA must concurrently address the needs of its longstanding patient base as well as the evolving challenges being presented by our newest war-wounded veterans." He said that of more than 8,000 service members medically evacuated from Iraq during the past four years or so, 13 percent had sustained

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Amputee Coalition of America (ACA) and successfully put into action at Walter Reed Army Medical Center. At that site, more than 100 “peer visitors”—themselves military amputees—have completed a one-day training, undergone evaluation and certification, and visited with more than 500 veterans of OIF and OEF who have lost limbs. By all accounts, veterans on both sides of the encounter have benefited. (See sidebar.)

Williams’ VA study is focusing on polytrauma—severe injuries and wounds that affect many organs and systems in the body. Usually the result of blasts, polytrauma can often involve limb loss as well as a complex web of other injuries: brain injury, spinal cord injury, nerve and organ damage, burns, wounds, fractures, vision loss, hearing loss.

Addressing brain injury is one of the key challenges for Williams’ group. Can a veteran who is himself coping with brain injury be an effective peer visitor?

“We’re trying to learn what modifications need to be made to the training to enable someone with a brain injury to fill this role,” says Williams. Smaller training groups and shorter sessions might be part of the answer. Another solution might be “reminders or templates during the visit to help them stay on track if they’ve got memory or attention problems.” For instance, visitors might use cue cards that outline what to say or not say, and perhaps alarm clocks to remind them to check their cards.

The research team, which also includes Pat Isenberg, MS, and Paddy Rossbach, RN, from the ACA and Dawn Ehde, PhD, from the University of Washington, is creating manuals for trainers and prospective peer visitors. They’re also working on materials for caregiver peer visitors—that is, parents or spouses of polytrauma-injured veterans who would visit other family caregivers coping with similar circumstances.



Rhonda Williams, PhD, discusses peer-visiting training materials with psychology intern Chris Miller, MA.

The VA study team is guided by an advisory panel of 10 polytrauma experts, six veterans who have been through polytrauma, and six caregivers. One of the questions the researchers are exploring is who qualifies as a “peer.” How closely do visitor and patient have to resemble each other—in terms of injury or military and personal background—for there to be a meaningful, therapeutic interaction?

“Everyone’s going to have a different constellation of injuries,” notes Williams. “We’re asking, do you have to have an amputation in order to be an effective peer visitor for an amputee? What if one had a burn and one didn’t? What if one had a brain injury and the other didn’t? What if one is an officer and the other is an enlisted person? What if one was injured in combat and the other in training?” Based on discussions so far, she says, many of these differences don’t appear to be crucial.

The researchers also have to sort out which types of health issues, besides brain injury, could be problematic in peer visitation. If a visitor has struggled with PTSD,

Program has good track record

Pat Isenberg, MS, chief operating officer of the Amputee Coalition of America and author of the group’s peer visitation training materials, says the program has been well-received at Walter Reed Army Medical Center (WRAMC), the Department of Defense facility where the majority of severely wounded soldiers from OIF and OEF undergo treatment and rehabilitation. Peer visitation ranked second only to overall rehabilitation in a recent WRAMC satisfaction survey covering 32 interventions, and the ACA has received lots of positive anecdotal feedback.

“Our most active peer visitors talk about how rewarding it is for them to see the progression of these injured young people from the ICU through painful rehab, to standing, and then to walking on their first prostheses,” says Isenberg. “I think one significant marker of the power of these interactions is the number of injured people who want to become peer visitors so they can give back as a way of paying it forward.”

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PTSD research conference to involve VA, DoD, NIH

VA has announced plans for a “consensus conference” with the Department of Defense and the National Institutes of Health so experts from the three agencies can exchange knowledge and work toward shared state-of-the-art approaches for research on posttraumatic stress disorder (PTSD). A date for the event has not yet been set.

On Oct. 18, the Institute of Medicine (IOM) released a report that endorsed the effectiveness of certain psychotherapy treatments—namely prolonged exposure therapy and cognitive processing therapy—but found inadequate evidence for the effectiveness of drug therapies for PTSD. VA commissioned the IOM research, which involved a review of 90 studies on PTSD treatments.

IOM study chairman Alfred Berg, MD, PhD, emphasized in a press conference that some drug treatments may in fact be quite effective, notwithstanding the lack of adequate scientific evidence to date on their behalf.

Acting Secretary of Veterans Affairs Gordon H. Mansfield said the IOM’s findings have important implications for the future of PTSD treatment for veterans and all Americans, and that VA will use them to guide future efforts. Concerning research, he noted: “VA research has led to the success of the therapies IOM believes are currently effective. And the work our researchers are already doing will help answer many of IOM’s questions on the effectiveness of pharmacological treatments.” Among other measures, Mansfield directed VA staff to work with DoD to evaluate early interventions such as the Army’s “Battlemind” training and the “Marine Operational Stress Surveillance and Training Program,” designed to help combat troops transition back to non-deployed and civilian status.

Photo courtesy of Duke University Medical Center



William S. Yancy Jr., MD, studies the effects of diet and exercise on obesity and its complications.

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low-carbohydrate, high-protein diet lost more weight over six months than people on a low-fat, low-cholesterol, low-calorie diet. The study was the first randomized, controlled trial of an Atkins-style approach to eating.

Yancy, also an assistant professor at Duke University Medical Center, was co-author on a study published in the *American Journal of Preventive Medicine* in 2005 that found that 68 percent of women and 73 percent of men using VA healthcare were overweight—somewhat higher than the figures for the general population. In other work, he has explored the effects of obesity on quality of life, drawing particular attention to the prevalence and impact of bodily pain in this population.

As part of the award, Johnson and Yancy will each receive \$125,000 over five years from VA’s Office of Research and Development in support of their research. ■

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slashing MRSA infection rates among their patients.

“There’s no code to bill Medicare for getting a swab on a patient and isolating him,” says Perencevich. “So hospitals have to justify these types of interventions continuously, and it’s put us behind the eight ball. You can spend \$50,000 to do a kidney transplant, but no one will give you \$10 to prevent that person from getting an infection.”

The VA researcher chaired a committee for the Society for Healthcare Epidemiology of America that published a guideline in the group’s Oct. 2007 journal. The guideline was titled “Raising Standards While Watching the Bottom Line: Making a Business Case for Infection Control.” “The goal is not to put economics first,” points out Perencevich. “But we have limited dollars, and we have to be smart about how we use them in order to improve quality.” ■

Studies reveal promising methods for regenerating brain cells

A team at the Durham VA and Duke University Medical Center has recently demonstrated two promising methods for coaxing stem cells within the hippocampus—the brain’s memory and learning center—to develop into new brain cells.

The researchers, led by Ashok Shetty, PhD, published results in the October issue of the *European Journal of Neuroscience* showing that infusions of a growth factor called FGF-2 into the brains of middle-aged rats led to an increase in brain cells and caused existing neurons to sprout new dendrites—the tentacles through which neurons exchange messages.

“We found considerably increased neurogenesis in the hippocampus following these infusions,” notes Shetty.

In other work, published in Aug. 2007 in the journal *Stem Cells*, Shetty’s group showed that implanting two types of brain-cell precursors into the brains of aging rats could also lead to the production of new cells responsible for learning and memory.

Shetty says there are still many scientific hurdles to clear before adopting these methods for clinical use, but they “provide proof of principle” that such approaches may be useful for increasing the addition of new neurons not only in aging brains, but after stroke, traumatic brain injury, or chronic drug-resistant epilepsy.

In the stem-cell study, the team used neural stem cells and glial-restricted progenitors, which are similar to stem cells but more restricted in their ability to self-renew and differentiate. Shetty says transplanting stem and progenitor cells into the brain appears to help mainly by releasing chemicals that activate the brain’s innate stem cells and improve the function of existing neurons. The transplanted cells themselves tend to become support cells within the brain, not neurons.

Shetty says some labs are working on getting stem cells to differentiate into neurons outside the organism, using a “cocktail” of neurotrophic factors, and then transplanting the neurons.

Bypassing the stem-cell approach altogether and infusing growth factors directly into the brain—as in Shetty’s other animal

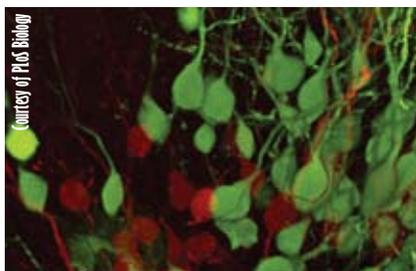


Bharathi Hattiangady, PhD (left), and Ashok Shetty, PhD, of VA and Duke University Medical Center.

experiments—might not prove practical in humans, he acknowledges, because of the invasiveness of the procedure. And administering them outside the brain would entail other challenges: “Some of these factors do not cross sufficiently through the blood-brain barrier to reach the brain targets, and they may have peripheral side effects.”

The ideal approach, he believes, may be refining the way in which stem and progenitor cells are prepared and transplanted. For instance, genetically engineering the cells to produce specific neurotrophic factors may prove beneficial. On the other hand, Shetty points out, the cells in their natural state seem to already make and secrete at least a handful of known brain-nurturing proteins, and could also be delivering “multiple unknown factors” that account for part of their effect.

In any case, the VA scientist says one of the main challenges that lies ahead is learning whether the cells are “capable of releasing the beneficial neurotrophic factors on a long-term basis”—which could be critical if they are to one day form the basis of therapies to regenerate aging or injured brains. ■



This slide shows dentate granule cells—the type of learning and memory cells successfully generated in animal experiments by Drs. Ashok Shetty and Bharathi Hattiangady and colleagues.

Find past issues of *VA Research Currents* on the Web at www.research.va.gov/resources/pubs/default.cfm

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combat-related eye trauma—the “highest percentage of eye wounded for any of the American wars of the past 100 years.”

Bob Filner (D-Calif.), chairman of the House Committee on Veterans’ Affairs, said: “The VA needs to be vigilant in its pursuit of treating veterans with mental health issues, brain injuries, amputations and other combat wounds. Our goal is to restore the capabilities of disabled veterans to the greatest extent possible and these VA research programs play a vital role in this process.” Subcommittee ranking member Jeff Miller (R-Fla.) added: “VA is world renowned for its medical research, which has a strong history of success and is credited with pioneering lifesaving therapies and treatments that have improved health care” for veterans and the nation.

Other witnesses at the hearing included representatives of the Paralyzed Veterans of America, Disabled American Veterans, and VA’s Office of Research and Development. Witnesses’ opening statements are available at <http://veterans.house.gov/hearings/hearing.aspx?newsid=118>. ■



As part of his polytrauma care, Marine Corps Cpl. Jason Poole, 22, spent well over a year in therapy with VA Palo Alto Health Care System occupational therapist Daniel Lita.

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could his own symptoms flare when he hears combat stories from a patient? Can a visitor still struggling with functional problems inspire someone in the early stages of recovery? What level of hearing impairment is enough to frustrate communication?

What’s clear is that peer visitation is therapeutic for both patient and visitor. “The people who have trained as peer visitors love fulfilling this role,” says Williams. “They feel they’re giving back, and it solidifies a sense of mastery for them. It highlights the progress they’ve made, and makes them feel the things they’ve learned the hard way can help the next guy.” ■