

New bionic ankle debuts at Providence VA

The first powered ankle-foot prosthesis, an important advance for lower-limb amputees, was unveiled July 23 at the Providence VA Medical Center. Garth Stewart, a 24-year-old Army veteran who lost his left leg below the knee following an injury in Iraq, demonstrated the new prosthesis.

Stewart walked in the prosthesis, which, unlike any other, propels users forward using tendon-like springs and an electric motor. The prototype device reduces fatigue, improves balance, and provides amputees with a more fluid gait. It could become commercially available as early as the summer of 2008.

MIT Media Lab Professor Hugh Herr, a VA-affiliated investigator since 2004, led the group that developed the ankle-foot. He is also a double amputee who tested his invention. "This design releases three times the power of a conventional prosthesis to propel you forward and, for the first time, provides amputees with a truly humanlike gait," Herr said. He compared using the device to walking on a moving walkway at an airport.

Stewart said that when he first began using the prototype, "One of the first things I noticed was a huge relief in back pressure."

Herr created the device through the Center for Restorative and Regenerative Medicine, a collaborative research initiative that includes the Providence

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Garth Stewart (right), wearing the new bionic ankle showcased at the Providence VA on July 23, greets a fellow veteran.



Jerome Siegel, PhD, and colleagues found that a loss of brain cells that make the peptide hypocretin is common to both narcolepsy and Parkinson's disease.

VA-UCLA team discovers link between Parkinson's disease, narcolepsy

Parkinson's disease is usually associated with symptoms relating to movement and muscle function: stiffness, slowness, tremors, difficulties walking and talking. Less well-known is that Parkinson's also shares symptoms with narcolepsy, a disorder marked by daytime sleep attacks, nighttime insomnia, and severe fatigue.

Now, researchers from the Greater Los Angeles VA Healthcare System and the University of California have discovered a bio-

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Study sheds light on mechanisms of common skin disorder

An international team spearheaded by researchers with VA and the University of California, San Diego (UCSD), have identified an inflammatory pathway that appears to play a key role in rosacea, a condition marked by reddish, pimply facial skin. The disorder affects nearly 14 million Americans.

The team, led by Richard L. Gallo, MD, PhD, found that over-production of two interactive inflammatory proteins results in excessive levels of a third protein that causes rosacea symptoms. “It’s like having lots of gasoline and a match,” said Gallo, chief of dermatology at the VA San Diego Healthcare System and UCSD. His group’s findings appeared in the Aug. 5 online edition of *Nature Medicine*.

Rosacea can have huge impact

Rosacea, often called adult acne, usually affects middle-aged people with fair skin. The skin over the cheeks and nose becomes red and pimply, with small blood vessels visible just beneath the surface. Alcohol—along with caffeine and spicy foods—tends to worsen the symptoms. “Psychologically, there are some people who are really devastated by it,” Gallo said in an interview with the *San Diego Union-Tribune*. Besides their dismay over their appearance, he said, “Some people think they’re alcoholics.”

This photo shows typical rosacea symptoms.



Rosacea tends to worsen over time and is generally cyclic, flaring up for a period of weeks to months, and then subsiding for a time. Antibiotics often bring some improvement, although, unlike acne, the condition isn’t associated with a skin infection by one type of bacteria.

Gallo’s group analyzed skin samples from volunteers with and without rosacea. In the rosacea samples, they found abnormally high levels of cathelicidins—antimicrobial peptides that are normally helpful in the body because they kill a wide range of bacteria and some viruses, and also activate other parts of the immune system. This class of peptides was first discovered in mammalian skin by Gallo’s lab in the 1990s.

Too much enzyme triggers problem

Abnormal over-expression of cathelicidins, however, can be a factor in skin disorders such as rosacea, suggests Gallo’s new study. His team found that the cathelicidin peptides prevalent in rosacea-affected skin—such as a form called LL-37—were different from those seen in normal skin. Further analysis showed that the abnormal peptides were due to elevated levels of an enzyme called SCTE, which converts cathelicidin precursor into its active, germ-fighting form. “Too much SCTE and too much cathelicidin leads to the abnormal peptides that cause the symptoms of this disease,” said Gallo.

‘Our findings may modify the therapeutic approach to treating rosacea, since bacteria aren’t the right target.’

—Dr. Richard Gallo

His VA-UCLA team, which collaborated with French and Japanese researchers, confirmed the one-two punch of cathelicidins and SCTE as the likely culprits in rosacea through several experiments in mice. For example, they were able to induce rosacea-like symptoms in mice by injecting them with cathelicidins and SCTE. They also showed that SCTE failed to produce a rosacea effect in mice lacking the gene that encodes for cathelicidins.

Gallo said certain antibiotics might help rosacea patients not because they kill bacteria but because they inhibit SCTE and other enzymes that work on cathelicidins. As a result of the new findings, he expects researchers will seek new approaches to treating the condition. “Our findings may modify the therapeutic approach to treating rosacea, since bacteria aren’t the right target,” he said. “Treatment could now be much more rationally designed.”

The researchers were supported by VA, the National Institutes of Health, the National Rosacea Society, and the Association for Preventive Medicine of Japan.

Veterans’ info on research website

The VA research website (www.research.va.gov) features educational materials for veterans considering taking part in VA studies. Click the “participating in a research study” link on the homepage.

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Adult-stem-cell therapy to be tested as adjunct to heart surgery

Researchers at the Salt Lake City VA and the University of Utah are gearing up to test whether patients undergoing bypass surgery for coronary artery disease will gain added benefit from an injection into the heart of adult stem cells, harvested from their own hip bone just prior to surgery. The trial will involve 18 veterans.

According to cardiac surgeon and lead investigator G. Russell Reiss, MD, the addition of stem cells should help boost heart function and improve quality of life. His team will use echocardiography, cardiac MRI and other tests to track outcome measures such as ejection fraction (EF), an indicator of how well the heart pumps blood. He expects bypass patients who receive the stem cell injection to see an increase in their EF of more than six percent, compared with bypass patients who receive only a placebo injection.

“Probably the most profound effect or benefit that patients could experience from an increase in EF is in their overall quality of life,” says Reiss. “People below 40 percent begin to realize real limitations in exercise and their ability to perform activities of daily living. Those with EFs in the 20s can be severely restricted or disabled. Fortunately, stem cells have been shown to help those with the lowest EFs the most. That is why we are focusing on patients with EFs less than 40 percent.”

Stem cells like ‘little fire rescue boats’

Scientists have learned that contrary to popular notion, the main way in which stem cells regenerate tissue is not by morphing into the type of cell that was lost or damaged—in this case, myocytes, or muscle cells. Rather, they promote the healing of other cells.

“They probably function best by helping save existing myocytes from death, not by creating new ones,” explains Reiss. “They seem to work like little fire rescue boats loaded with cytokines, growth factors and anti-apoptotic factors that they can deliver to highly specific areas of injury and inflammation, helping to stabilize the whole area at a cell-to-cell level.”

Reiss said the stem cells also seem to “stabilize the cytoskeleton of the heart and act as a ‘functional patch’ to maintain the proper geometry of the heart, which is very critical to the overall performance of the heart as it undergoes remodeling from injury.”

The phase 1 trial, funded by VA, will get under way even as Reiss and colleagues continue to perform animal experiments to further expand and refine knowledge of how the stem cells work. “Regenerative medicine, which includes stem cell therapies, is a highly translational field and there is a great deal of bench to bed-



G. Russell Reiss, MD, will be leading a clinical trial testing the benefits of adult stem cell implantation—along with heart bypass surgery—for patients with coronary artery disease.

side and back to the bench that takes place,” he said. “Most investigators involved in these trials will need expertise both in the animal lab and with conducting human clinical trials.” He emphasized that human trials are conducted only after the therapy has been shown to be safe in animals.

The clinical trial will involve a graded approach in which higher doses of stem cells—up to 100 million cells—will be administered to patients enrolled in later stages of the study, after lower doses have proved thoroughly safe. ■

VA spinal cord injury conference

VA researchers will be among those attending and teaching at the 16th Educational Symposium on Spinal Cord Injury (SCI) Medicine, presented on Nov. 2, 2007, in Dedham, Mass., by the Spinal Cord Injury Service of the VA Boston Healthcare System. The event will cover the latest information on SCI care, rehabilitation and research, from identifying microorganisms in SCI-related infections to understanding psychosocial issues in returning soldiers with SCI. The registration deadline is Oct. 26. For more information call (857) 203-5128 or (857) 203-6574.

PARKINSON'S (from pg. 1)

logical basis for the link: Both Parkinson's and narcolepsy patients have major deficiencies of brain cells that make a chemical called hypocretin. The findings were published in the June issue of *Brain*.

"When we think of Parkinson's, the first thing that comes to mind are the motor disorders associated with it," said Jerome Siegel, PhD, chief of neurobiology research at the VA Medical Center in Sepulveda and professor of psychiatry and biobehavioral sciences at UCLA. "But sleep disruption is a major problem in Parkinson's, often more disturbing than its motor symptoms. And most Parkinson's patients have daytime sleep attacks that resemble narcoleptic sleep attacks."

In fact, said Siegel, Parkinson's disease is often preceded and accompanied not only by daytime sleep attacks and nighttime insomnia, but by REM sleep disorder, hallucinations and depression—all of which appear in narcolepsy.

Direct relationship between cell loss and Parkinson's disease progression

In the study, the researchers examined 16 human brains from cadavers — 5 from normal adults and 11 in various stages of Parkinson's. They found an increasing loss of hypocretin cells with disease progression—up to a "massive" 62-percent loss in stage 5 Parkinson's. Said Siegel, "That leads us to believe the loss of these cells may be a cause of the narcolepsy-like symptoms of [Parkinson's] and may be ameliorated by treatments aimed at reversing the hypocretin deficit."

While no hypocretin treatments are currently available, Siegel said he hopes such therapies will be brought to clinical trials within the next few years. "We have had success with administration of hypocretin to dogs with narcolepsy," he noted.

In 2000, the same group of researchers found that human brains from narcoleptics, compared to normal brains, had up to 95-percent fewer hypocretin neurons. Before then, hypocretin had been linked by scientists to narcolepsy in animals, but its role in human narcolepsy had not been established.

More than one million people in the U.S. have been diagnosed with Parkinson's disease. Narcolepsy is less common, affecting about 150,000 people in the U.S., or 1 in 2,000 people. Patients are excessively drowsy during the day. They fight the urge to sink into a deep sleep while at work, walking around, or even behind the wheel of a car. At night, their sleep is frequently interrupted. Other symptoms include cataplexy—loss of muscle tone, where patients can suddenly lose consciousness and fall down—and vivid

Which providers are most likely to order inappropriate prostate screenings?

Past research in both VA and non-VA settings has shown that the prostate-specific antigen (PSA) test to screen for prostate cancer is often performed for patients for whom the test has shown no benefit. Now, researchers who analyzed VA data on more than 230,000 PSA tests have profiled—by gender, age and other characteristics—which providers are more likely to order inappropriate tests. Their report appeared in the July 9 *Archives of Internal Medicine*.

A team led by B. Price Kerfoot, MD, EdM, of the VA Boston Healthcare System and Harvard Medical School, analyzed data from 105,765 male patients who were treated at VA facilities in New England from 1997 to 2004. Information about the patients and the 1,552 health care clinicians who ordered PSA tests was gathered from VA databases. Inappropriate screening was defined as PSA testing in patients older than 75 or younger than 40 who had not been diagnosed with prostate cancer, were not taking prostate cancer-specific medications or had not undergone related procedures.

Most guidelines for clinical practice do not recommend routine PSA screening for men who are younger than 40 or older than 75, or who are expected to live less than 10 years. "To our knowledge, there is currently no solid evidence that PSA screening provides any health benefits for these patient populations," wrote Kerfoot and his coauthors. "Rather, it imposes substantial psychological and financial costs and may lead to diagnostic and therapeutic procedures of questionable benefit."

According to the study, of the 232,302 PSA tests ordered during the study period, 16.1 percent were inappropriate, with 15.3 percent performed in patients older than 75 years and the remainder in patients younger than 40 years. Of the clinicians who ordered inappropriate tests, 51.3 percent were male, 79.4 percent were physicians, 53.4 percent were trainee physicians and 8.2 percent were urologists. "Practitioners who were urology specialists, male, infrequent PSA tests-orderers and affiliated with specific hospitals

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and dreamlike hallucinations that occur immediately before or after sleep. Treatment often includes stimulants and antidepressants.

Funding for Siegel's study was provided by VA and the National Institutes of Health. His coauthors were Thomas C. Thannickal, PhD, and Yuan-Yang Lai, PhD, both with VA and UCLA. ■

Wheelchair innovator to be honored by Multiple Sclerosis Society

Rory Cooper, PhD, director of the VA Center of Excellence in Wheelchairs and Associated Rehabilitation Engineering—part of the Human Engineering Research Laboratories at the University of Pittsburgh and VA Pittsburgh Healthcare System—will receive the 2007 daVinci Lifetime Achievement Award on Sept. 28 from the Michigan Chapter of the National Multiple Sclerosis Society.

Cooper is recognized as a leading expert on wheelchair design and mobility research. He holds several patents, and is the author or coauthor of more than 150 journal articles, as well as the author of two books: *Rehabilitation Engineering Applied to Mobility and Manipulation*, and *Wheelchair Selection and Configuration*.

Cooper's career path took shape after he became permanently disabled in 1980. A U.S. soldier stationed in Germany, he was riding his bicycle when he was struck by a bus and then run over by a truck. He suffered a T7-T8 spinal cord injury and underwent months of hospitalization and extensive rehabilitation. He went on to earn advanced degrees in engineering, concentrating on bioengineering, and focused much of his early work on the design of racing wheelchairs. Cooper eventually became the first chair of the first department of rehabilitation science and technology in the U.S., at the University of Pittsburgh. He has been a VA investigator since 1994.

An Olympic hopeful in track during his Army days, Cooper eventually fulfilled his Olympics dream by winning a bronze medal in the 1988 international Paralympics. He still competes in VA's National Veterans Wheelchair Games each year—mainly, he says, “to set a goal for myself each year in trying to stay fit, and to be a role model for newly injured people so they have the opportunity to see that you can go back to



Photo by Christine Heiner

Rory Cooper, PhD, of VA and the University of Pittsburgh, will be honored by the National MS Society on Sept. 28 for his “lifetime of significant contributions to advancing accessibility.”

work, you can participate in sports, and you can have a full life.”

For more information on Cooper's center, visit www.herl.research.va.gov. For more details on the DaVinci awards event, sponsored by General Motors and benefiting the National Multiple Sclerosis Society, visit www.davinciawards.org. ■

‘[I want] to be a role model for newly injured people so they have the opportunity to see that you can ... have a full life.’

—Dr. Rory Cooper

VA researchers in the media

Jill E. Bormann, PhD, RN, who conducts research at the VA San Diego Healthcare System on the use of mantram repetition—a type of meditation—for easing stress and anxiety, was interviewed in a recent National Public Radio broadcast.

Lisa Schwartz, MD, MS, and **H. Gilbert Welch, MD**, of the VA Outcomes Group, a health-services research team based at the White River Junction VA Medical Center, were featured in a July 10 *New York Times* article titled “Doctors Balk at Cancer Ad, Citing Lack of Evidence.”



Hugh Herr, PhD, the inventor of the Powered Ankle-Foot and himself a double below-the-knee amputee, demonstrates the device at the Providence VA Medical Center.

‘This design releases three times the power of a conventional prosthesis. ...’

—Dr. Hugh Herr

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VA Medical Center, Brown University and MIT. The center was initially funded in 2004 with \$7.2 million from VA, and an additional \$6.9 million from the agency is now funding construction of a new state-of-the-art research building to house the center on the Providence VA campus.

Goal of center is ‘biohybrid limb’

The center boasts a team of researchers with expertise in tissue engineering, orthopedics, neurotechnology, prosthetic design and rehabilitation. Their aim is to eventually create “biohybrid” limbs that integrate biological and manmade materials and function almost like natural limbs. Part of the effort involves research led by John Donoghue, PhD, on a system called BrainGate that allows movement signals from the brain to be picked up by a tiny implanted sensor and decoded into commands for prosthetics or other robotic and electronic devices. Other research is aimed at promoting osseointegration, an innovative surgical technique that allows prostheses to be anchored directly into the bone of the residual limb.

Stewart, the veteran who demonstrated the new bionic ankle on July 23, said he is looking forward to seeing more research-driven advances: “What’s really exciting is that they want, within a couple of years, to be able to graft this device to a human skeleton and then run interfaces between the brain and the nerves, so you can feel it and move it by thinking.”

‘Creativity, ingenuity on behalf of amputees’

Joel Kupersmith, MD, chief research and development officer for VA, remarked how the new ankle is a prime example of how VA research is advancing prosthetics care for veterans—especially those returning from Iraq and Afghanistan.

“Up to now, prosthetic devices have not been able to duplicate the complex functions of our feet and ankles as we walk and run,” he said. “The ingenious computerized design of this new prosthesis changes all of this, as it constantly ‘thinks’ and responds, allowing the person to walk or run in a more natural and comfortable way.”

Michael E. Selzer, MD, PhD, director of Rehabilitation Research and Development for VA, added: “Hugh Herr and his Media Lab group are well-known for their scientific ingenuity and creativity on behalf of amputees. This new technology represents rehabilitation research at its finest, and is yet another milestone in VA’s long history of outstanding achievements in this area.”

More coverage on next page

An earlier VA milestone in foot prostheses...

In the 1960s, Ernest Burgess, MD, PhD, then chief of the amputee clinic at the VA hospital in Seattle, led a study on the practice of fitting amputees with prosthetic devices immediately after surgery, a technique that was eventually adopted nationwide. His team also went on to pioneer computer-assisted software used in prosthesis fitting.

But Burgess, who passed away in 2000, was perhaps best known for his role in developing the revolutionary Seattle Foot. His team at VA and the University of Washington collaborated in the 1980s with engineers at Boeing Aerospace to develop the device, which was introduced in 1985 and by the late 1990s was worn by as many as 120,000 amputees worldwide. The innovative artificial foot greatly enhanced amputees' ability to run and participate in sports, and merited a Presidential Design Achievement Award in 1984.

The Foot, which later gave rise to the development of a complete Seattle Limb System, took advantage of lightweight, responsive materials that captured an amputee's natural movement. It used a patented spring, named a monolithic keel, made of a material called Delrin, manufactured by DuPont. (The company produced a 1988 TV ad for the device showing Bill Demby, who had lost both legs below the knee in Vietnam, playing basketball with two Seattle Feet.) The spring helps the user push off in taking a step. It does so by storing energy when the foot initially steps down, and then releasing the energy at the ball of the foot when the heel leaves the ground as the step is completed.



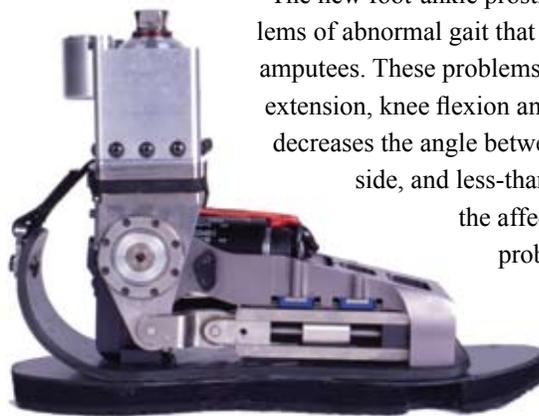
Professor Hugh Herr addresses the audience at the July 23 media event at the Providence VA.

How does the new ankle-foot benefit amputees?

The device being developed by Herr's group (*see article starting on page 1*) is the first powered ankle-foot prosthesis. It propels the wearer forward, thanks to a unidirectional spring and force-controllable actuator. It also varies its stiffness as users walk over irregular terrain. These two properties enable the device to mimic the action of a biological ankle. Conventional ankle-foot prostheses, on the other hand, are passive. This causes users to expend up to 30 percent more energy during walking than non-amputees. As a result, they typically walk at speeds that are 30 to 40 percent slower.

Herr's team recorded improvements from 7 to 20 percent in the "metabolic economy" of research volunteers who wore the device—even though it is two times heavier than conventional prosthetic models.

The new foot-ankle prosthesis is also expected to alleviate problems of abnormal gait that are common among below-the-knee amputees. These problems include greater-than-normal hip extension, knee flexion and ankle dorsiflexion—a movement that decreases the angle between the foot and leg—on the unaffected side, and less-than-normal flexion of the hip and knee on the affected side. Studies have associated these problems with long-term complications such as low back pain and osteoarthritis. ■



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had significantly higher levels of inappropriate PSA screening. Compared with attending physicians, nurses and physician assistants had significantly lower levels of inappropriate screening,” the authors wrote.

The article also notes that the percentage of inappropriate PSA screening increased significantly with the age of male providers, and suggests a possible explanation: “The cause of these sex and age differences is not clear. It is possible that, as they age, male health care providers increasingly empathize with their older male patients over prostate cancer concerns. Their ‘prostatempathy’ may then lead to more aggressive screening in these older male patients.”

Kerfoot emphasizes that “whether their healthcare provider is suffering from ‘prostatempathy’ or not, patients older than 75 should be informed that the clinical practice guidelines do not recommend further prostate screening with PSA. The patient and his care provider can then decide together whether to continue screening.”

The researchers suggest that both patient and provider education may be part of the solution, although Kerfoot notes that computerized clinical reminders for providers have produced mixed results in terms of their effectiveness. With funding from a VA Career Development Award, he is currently working to develop Web-based education for doctors that he believes may help promote the translation of evidence-based guidelines into clinical practice. ■



Robotic stroke therapy put to test

Allen Wright, a former Navy aircraft mechanic who suffered a stroke in 2000, exercises his affected arm with the use of a robot called the MIT-Manus. Looking on is exercise physiologist Tim DeHaan. Wright, a patient at the Baltimore VA, is among more than 150 veterans taking part in a VA-funded clinical trial at Baltimore and three other VA sites—West Haven, Gainesville and Seattle—comparing robotic therapy with intensive non-robotic therapy for improving motor function in chronic stroke patients.