

VA has key role in 80-site blood pressure study

The National Institutes of Health has awarded \$15 million to William Cushman, MD, chief of preventive medicine at the Memphis VA Medical Center, to lead a network of 20 VA sites in the Systolic Blood Pressure Intervention Trial.

The trial will test whether lowering systolic blood pressure (the top number in a blood-pressure reading) beyond current guidelines can further curb heart attacks, strokes and other cardiovascular events—as well as kidney disease—in older people. Experts believe this may be the case, based on prior observational studies.

Along with 1,500 veterans at the VA sites, some 6,000 volunteers will take part in the \$114 million trial. About a third of the volunteers will also undergo tests to check the effects of lower blood pressure on their memory and thinking. Hypertension is a well-known cause of vascular dementia and some studies have linked it to Alzheimer's disease (*see sidebar on pg. 6*).

Study volunteers will take commonly prescribed blood-pressure drugs to reach one of two systolic goals—under 140

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Exercise physiologist Jeff Beans checks the blood pressure of James McMahon, a participant in a recent stroke study at the Baltimore VA.



Brain scans yield potential biomarker for PTSD

Research at Minneapolis VA used high-tech method for capturing neuron activity

Using a super-fast scanner that captures cross-talk between groups of neurons in the brain, VA researchers and colleagues have identified a potential biological marker of PTSD. The findings appeared in the Jan. 20 *Journal of Neural Engineering*.

More than 70 veterans with PTSD and 250 people with no mental diagnoses took part in the study. Using magnetoencephalography (MEG), a noninvasive scan that

detects the tiny magnetic fields created when brain cells “fire,” the researchers found a pattern of activity unique to PTSD. They were able to differentiate between those with PTSD and healthy controls with better than 90-percent accuracy.

“These findings document robust differences in brain function between the PTSD and control groups that can be used for

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BIOMARKER (from page 1)

differential diagnosis,” said neuroscientist Apostolos Georgopoulos, MD, PhD, who led the study along with psychologist Brian Engdahl, PhD. Both are with the Brain Sciences Center at the Minneapolis VA Medical Center and University of Minnesota. The program is supported in part by the American Legion.

Georgopoulos said MEG technology could also be used to track disease progression and the effects of therapy

He noted that if the PTSD biomarker holds up in further study, it may eventually become one of the tools used by VA and the Department of Defense to help determine the medical status of service members and veterans. This could apply especially when symptoms of PTSD and brain injury overlap, making it more difficult for doctors to make accurate diagnoses.

The dome-shaped MEG scanner captures bursts of neuron activity that last only milliseconds. By comparison, a functional MRI scan takes three seconds to make a picture. When researchers overlay data from MEG scans on a map of the brain, they can

Eavesdropping on brain cells—Dr. Apostolos Georgopoulos, a neuroscientist at the Minneapolis VA, has helped pioneer the use of magnetoencephalography to detect brain disorders. The MEG scanner records the tiny magnetic fields created when brain cells send messages to each other.



A PTSD biomarker could be used to aid diagnosis or track therapy's effects.

show abnormalities—even subtle ones—as patches of color, indicating precisely which areas of the brain may be damaged.

The researchers found that in veterans with PTSD, the working connections among groups of brain cells were much stronger on the right side of the brain, in an area known as the parieto-temporal region. Georgopoulos: “This shows a strong miscommunication pattern of this area with the rest of the brain. It is possibly related to the permanent and painful memories that are characteristic of PTSD. Veterans who have recovered from PTSD still show this pattern, but not as strongly.”

In a smaller sample, veterans with mild brain injuries—most commonly from

blasts—showed unfocused, diffused miscommunication among many brain regions, along with symptoms such as headaches and dizziness. Blast-exposed veterans who no longer had such symptoms showed the same diffuse pattern. The researchers say this may be evidence of the long-lasting effects of some mild brain injuries.

The group now plans to study larger groups of veterans with PTSD as the sole mental diagnosis and compare their MEG scans with those of healthy volunteers. The scientists already have further studies under way with patients who have PTSD plus brain injury or other problems, such as depression or alcohol abuse.

The PTSD research follows other work in which Georgopoulos’ team used MEG to detect distinct patterns for conditions including Alzheimer’s disease, multiple sclerosis, schizophrenia and chronic alcoholism. —

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



Robotic system may put more tasks within wheelchair users' reach

Researchers at the Human Engineering Laboratories (HERL), a joint program of VA and the University of Pittsburgh, are building a system they say will enable wheelchair users with limited use of their hands to do a range of everyday tasks—for example, taking food out of the refrigerator and heating it in a microwave, or picking up a book from across a table.

The system is called the perMMA, short for Personal Mobility and Manipulation Appliance. Simply put, it's a power wheelchair fitted with robotic arms. At the business end of the arms are grippers with force and temperature sensors.

As the project stands today, the arms are generally controlled not by the wheelchair user but by a helper at a remote location, via the Internet. The wheelchair has 3D webcams that allow the assistant to see the user's surroundings. When a user signals for help, the assistant can steer the arms to complete a task.

But HERL engineers are working on extending full control to the person in the

wheelchair. A variety of technologies are being explored—for example, voice activation, or a video tracking system that would have the robotic arms follow the user's head movement. Another approach, suitable for those with some use of a hand, would have the robotic arms respond to light touch; the arms and their payload would seem weightless to the user. Yet another option down the road might be a brain-computer interface that would enable users to control the arms directly with their thoughts.

In testing so far, users—generally with help from the assistants—have been able to accomplish tasks such as picking up a key, getting a drink and switching on a light.

HERL director Rory Cooper, PhD, well-known as an assistive-technology innovator, wheelchair athlete and advocate for people with disabilities, acknowledges that it's important to eventually enable users to work the system by themselves. At the same time, though, he points out that “we are in uncharted waters, given the complexity of

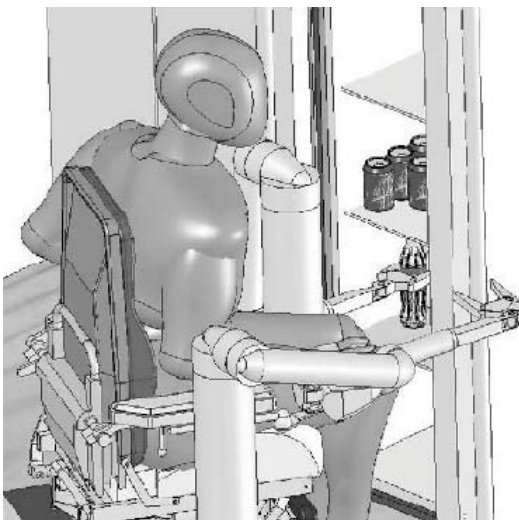


Engineer Juan Vazquez remotely operates the robotic arms on the perMMA as he views the user's surroundings, via wheelchair-mounted webcams, on a computer screen.

the tasks that people would like to perform, and the fact that robotic systems have not yet been designed to work on real activities of daily living in the real world.”

He notes that the remote assistant in the perMMA system would act as an “extender” to in-person assistant hours that many wheelchair users rely on. “Most people receive only a maximum of eight hours of personal assistance a day,” says Cooper. “This leads to a very structured life. We hope that with a combination of personal assistance, robotics and remote assistance, people will have greater independence through having more options and choices in their daily lives.

“Independence,” he stresses, “is about being able to do what you want when you want, not necessarily about doing it yourself.” —



The perMMA would help wheelchair users who have limited use of their arms and hands.



U.S. soldiers in action in Diyala province, Iraq, in 2008.

Mental diagnoses tied to higher use of non-mental VA care in OEF/OIF study

A database study of nearly 250,000 veterans of the wars in Iraq and Afghanistan who used VA care for the first time between 2001 and 2007 found that those with mental-health diagnoses used non-mental-health medical services in VA at higher rates than those without mental health disorders. The results appeared in the January 2010 *Journal of General Internal Medicine*.

Veterans with PTSD used non-mental services at a 91 percent higher rate than those without mental health diagnoses. Veterans with a mental health diagnosis other than PTSD, such as depression, had a 55 percent higher use rate than those without mental health diagnoses. The overall results are consistent with studies of veterans from earlier wars, says lead author Beth Cohen, MD, MAS, a staff physician at the San Francisco VA Medical Center. “What we don’t know from this data,” she says, “is whether these veterans are using medical care more often because they simply have more medical diseases, or because they need help with mental health concerns but seek care in other medical settings” because of the stigma associated with mental health treatment.

The researchers now plan to evaluate the effects of different models of care delivery on utilization. One such model is the OEF/OIF Integrated Care Clinic at the San Francisco VA, where all patients, whether or not they screen positive for a mental health concern, are seen by primary care, mental health and social work providers, potentially reducing the stigma of seeking mental health care. —

Low-carb diet edges out weight-loss drug for lowering blood pressure

In a head-to-head comparison, two popular weight-loss methods proved equally effective at helping overweight and obese veterans shed pounds. But, in a surprising twist, a low-carbohydrate diet proved better at lowering blood pressure than the weight-loss drug orlistat, reported researchers with VA and Duke University Medical Center in the Jan. 25 *Archives of Internal Medicine*.

The findings send an important message to those with hypertension who are trying to lose weight, said lead author William S. Yancy Jr., MD. “If people have high blood pressure and a weight problem, a low-carbohydrate diet might be a better option than a weight-loss medication. It’s important to know you can try a diet instead of medication and get the same weight-loss results with fewer costs and potentially fewer side effects.”

The 146 men and women in the year-long study had a range of health problems typically seen with obesity—diabetes, high blood pressure, high cholesterol, arthritis. Nonetheless, they saw impressive results from the study treatments: The average weight loss for both groups was nearly 10 percent of body weight. Yancy attributed much of the success to the group counseling that was offered to both sets of patients, noting that it may have played an especially key role for those taking orlistat, the gastrointestinal side effects of which can be mitigated by strict adherence to a low-fat diet. “People tolerated orlistat better than I expected,” said Yancy. “We counseled people on orlistat in our study fairly extensively about the low-fat diet.”

The two methods proved equal not only for weight loss, but also for reducing levels of cholesterol and blood sugar. With regard to blood pressure, though, there was a distinct edge to the low-carb approach. Some 47 percent of patients in the low-carb group were able to decrease or discontinue their blood pressure medication, while only 21 percent of the orlistat group were able to do so. Yancy says the mechanism is unclear. “While weight loss typically induces improvements in blood pressure, it may be that the low-carbohydrate diet has an additional effect.” He said the physiologic effect may be the topic of future studies.

The take-home message, said Yancy, is that many diet options are proving effective at weight loss, but patient counseling may be a critical piece of the puzzle. “It is clear now that several diet options can work, so people can be given a choice of different ways to lose weight. But more importantly, we need to find new ways to help people maintain their new lifestyle.” —



Dr. Matthew Wilson says a gene-transfer method his lab is developing could come to play a key role in drug discovery and gene therapy.

New gene technique could speed drug discovery

Drug discovery in biomedical labs worldwide may benefit from a new gene-insertion method being developed at the Michael E. DeBakey Veterans Affairs Medical Center and Baylor College of Medicine in Houston. The technique was described in a Jan. 6 online report in the *Proceedings of the National Academy of Sciences*.

Until now, researchers have generally been able to insert only one gene at a time into cells or lab mice to study its effects. The new method will enable them to insert several genes at once. Lead researcher Matthew H. Wilson, MD, PhD, says the new gene-transfer technique “allows you to ask a whole new level of questions that you couldn’t ask before.”

By way of example, he says scientists who want to study a certain receptor—a

protein in cells that binds with other specific molecules—can now easily create a cell line tailored to their line of research. By inserting multiple protein-coding genes in one operation, they can in effect custom-design the cells they need. “Sometimes you need the receptor and a few signaling molecules downstream to see an effect in the cell,” explains Wilson. “This would allow you to put all of that in at one time and make a cell line that would be appropriate to study the biology of whatever pathway you’re interested in.”

The new method uses carrier genes called transposons. Discovered in the 1950s, transposons are also known as “jumping genes” because they spontaneously hop around to different spots on the DNA strands that make up an organism’s genome.

Several different transposons have been studied in recent years because they offer an efficient way to ferry new genes into the DNA of cells or lab animals. Wilson’s lab has focused on one transposon in particular, known as piggyBac. In their experiments, the team used the gene and its related enzyme to efficiently transfer up to eight genes at once into human kidney cells.

Besides drug discovery, transposons hold promise for gene therapy. They are seen as potentially safer, faster and more cost-effective than current methods that use viruses to transfer beneficial genes into patients’ DNA.

One scientific hurdle that must be cleared before transposons can be used in humans is

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mmHg (standard group) or under 120 mmHg (treatment group). The treatment group will take about three or four medicines, while those in the standard group will take an average of two drugs. Patients in both groups will be followed for up to six years. The study is not designed to compare drugs—only medical strategies. Doctors will choose which drugs to prescribe based on individual patient factors.

Systolic pressure is good predictor of vascular trouble

High blood pressure affects more than 50 million U.S. adults and is a top cause of stroke, heart disease, kidney failure and other conditions. Blood pressure measurements are written with the systolic reading above or before the diastolic reading, such as 120/80 mmHg. Systolic pressure is the pressure on the arteries when the heart beats and pumps blood through the arteries. Diastolic pressure is the pressure when the heart is filling with blood between beats. Both numbers are important, but research has found that high systolic pressure is an especially potent predictor of vascular problems, especially among older people. All the participants in the new trial will be age 55 or older.

Commenting on the newly funded trial, NIH officials said that if the approach of maintaining lower systolic pressure proves successful, it could mean “hundreds of thousands fewer heart attacks and strokes each year in the United States alone.”

VA’s Cushman is recognized as one of the nation’s foremost experts on hypertension treatment. He co-led the landmark ALLHAT study, an NIH-VA collaboration that was the largest hypertension clinical trial ever conducted. The main results, published in 2002, showed that conventional diuretics were better than newer, more expensive medicines for treating hypertension. —

Artificial lens may help cataracts

An auto-focusing artificial lens that turns from liquid to gel after being implanted in the eye may one day be a leap forward in cataract care, says the inventor of the technology.

Nathan Ravi, MD, PhD, and his team at the St. Louis VA and Washington University are developing a lens based on nanomaterials that mimics the soft, pliable lens of the human eye. In cataracts, the normally transparent lens becomes cloudy. Even advanced cases can usually be fixed through surgery, in which a prosthetic lens is placed inside the eye. But current prosthetic lenses have only limited focusing power, and most patients still need to wear glasses.

According to Ravi, his lab’s artificial lens could potentially restore natural focusing ability. Plus, it could be placed



Cataracts affect nearly 22 million Americans age 40 and older, and nearly half of those over 80.

in the eye through a technique that is less invasive than current cataract surgery.

Besides fixing cataracts, the lens could potentially be used to correct near- or farsightedness. That would be an elective procedure, says Ravi, similar to laser eye surgery, whereas cataract procedures are medically necessary to preserve vision.

see **LENS** on next page

Can hypertension drugs thwart Alzheimer’s?

Medications known as angiotensin receptor blockers (ARBs)—brand names such as Atacand or Avapro—are used mainly to treat high blood pressure and heart failure because they block a hormone that narrows blood vessels. Now, a team at the Bedford (Mass.) and Boston VA medical centers has found that the drugs may also help prevent dementia, adding to similar results from some previous studies. The team reported their findings in the *British Medical Journal* on Jan. 12.

The study, based at VA’s Center for Health Quality Outcomes and Economic Research, analyzed the records of more than 800,000 older veterans who had been treated for hypertension or heart disease. They found that those taking ARBs were up to 24 percent less likely to develop dementia than those taking other drugs. Moreover, of patients who had Alzheimer’s disease at the study’s outset, those on ARBs were half as likely to enter a nursing home, compared with those taking ACE inhibitors or other heart drugs.

In an interview with *Business Week*, senior author Benjamin Wolozin, MD, PhD, with VA and Boston University, said improved blood flow to the brain is the likely mechanism behind the drugs’ apparent cognitive benefits. “If you get no blood to the brain, you’re not going to think well,” he said.

Wolozin pointed out that randomized clinical trials will be needed to test whether ARBs are truly responsible for the Alzheimer’s-thwarting effect seen in his group’s large database study. Meanwhile, he cautioned that the new evidence is not enough to warrant routine clinical use of ARBs to halt dementia, adding that the drugs could pose significant side effects for some patients, such as drops in blood pressure that lead to falls. —

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To help develop their artificial lens, Ravi's group invented a robotic device that mimics the action of the ciliary body, the muscle in the eye that stretches the lens and thus enables it to focus. The octopus-like machine, with eight stainless-steel arms, simulates the natural movement of the eye as it shifts focus. In real life, says Ravi, this movement "occurs almost instantaneously and imperceptibly."

By measuring the dynamic forces involved in focusing, the researchers have been able to design an artificial lens that responds to the ciliary muscle as would a natural lens.

"This [device] is unique to our lab and has enabled us to characterize the time-dependent mechanical response of the lens," says Ravi.

The group has also developed a related product to replace the vitreous gel, the clear "jelly" that fills the space behind the lens. In a procedure called a vitrectomy, doctors remove this part of the eye to treat a number of vision-threatening conditions. Ravi said

Eye-opener—

Engineer Paul Hamilton (standing) and ophthalmologist Nathan Ravi, chief of staff at the St. Louis VA, collaborated to build a robotic "lens stretcher" that mimics the function of the ciliary muscle inside the human eye. The machine helps Ravi's team learn how a natural lens focuses and has guided their design of a synthetic replacement lens made from a nanocomposite hydrogel (seen in photo below).

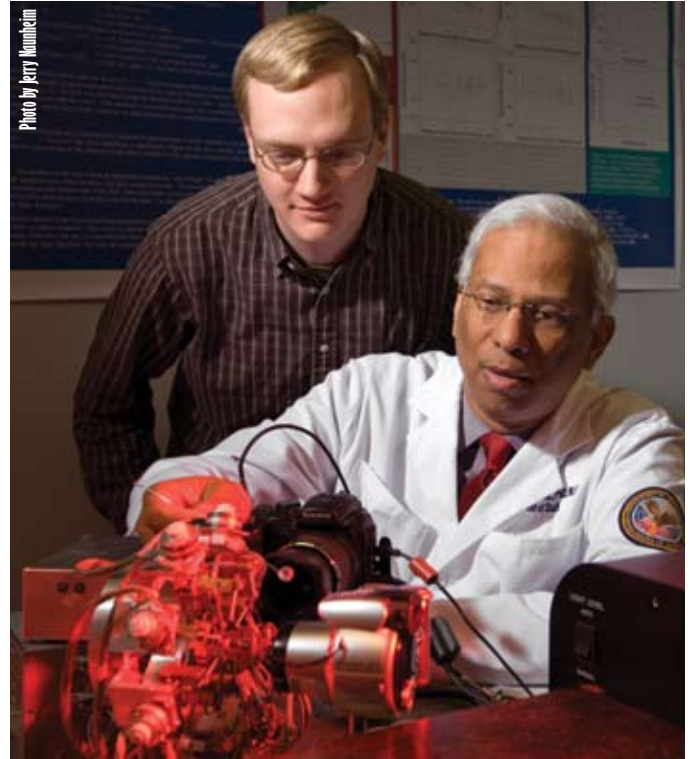


Photo by Jerry Mannheim

the hydrogel his group is now testing in rabbits may be more biocompatible than the vitreous replacements currently in use. He said the nano-gel could also potentially be used to hold the retina in place in cases of traumatic eye injury. ➔

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learning how to target these "jumping genes" and their payload to exact locations in the genome. Such precision would be critical for patient safety, as it would help avoid unforeseen genetic changes. Wilson says his lab is now working on solving that problem.

The recipient of Career Development funding from VA, Wilson specializes in nephrology research. He hopes to eventually develop a treatment for an inherited kidney disease called Alport Syndrome, which affects 1 in 5,000 people. His group's breakthrough in transposon-based gene transfer came as they sought the best ways to deliver genes to the kidneys of mice. ➔



Photo by Jerry Mannheim

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**Inside: New gene technique
could speed drug discovery**

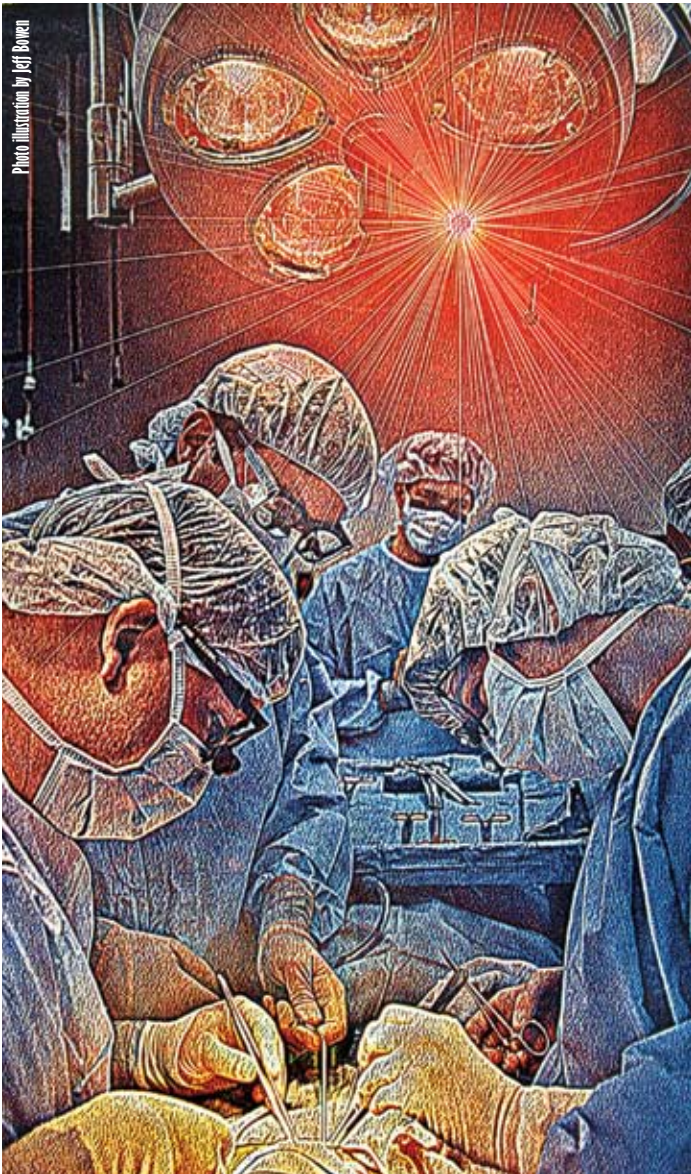


Illustration based on a photo of surgery at the Little Rock VA Medical Center.

Study compares surgery antiseptics

Patients whose surgeons use chlorhexidine-alcohol rather than povidone-iodine to cleanse their skin before surgery are about 40 percent less likely to get an infection around the incision, according to a study of 849 surgeries at four VA medical centers and two non-VA hospitals. The results appeared in the Jan. 7 *New England Journal of Medicine*.

The overall rate of surgical-site infection with the alcohol preparation was 9.5 percent, compared with just over 16 percent with povidone-iodine.

“The results of this study are extremely significant since two-thirds of surgical-site infections are confined to the incision,” noted lead author Rabih Darouiche, MD, of the Michael E. DeBakey VA Medical Center and Baylor College of Medicine in Houston.

Despite routine skin cleansing with povidone-iodine—the current standard of care—surgical-site infection occurs in up to half a million surgery patients each year in the United States. The Centers for Disease Control and Prevention has recommended chlorhexidine-based preparations for other medical uses but has not made recommendations for preventing surgical infections.

An editorial by Richard Wenzel, MD, of Virginia Commonwealth University that accompanied the article by Darouiche’s team in the *New England Journal of Medicine* said that the study “supports the value of a relatively inexpensive ... program, which was remarkably effective. ... The weight of evidence suggests that chlorhexidine-alcohol should replace povidone-iodine as the standard for preoperative surgical scrubs.”