

Understanding the effects of blasts on the brain

It's a scientific question driven by the hard realities of today's global war on terror: What happens to the brain of someone exposed to a blast?

The answer is likely to come not from the battlefields of Iraq and Afghanistan, but from research labs thousands of miles away—such as that of biomedical engineer Pamela VandeVord, PhD, with VA and Wayne State University in Detroit. She is one of a small but growing number of researchers studying the biological effects of blasts on the brain.

With funding from VA, VandeVord's team studies brain cells that have been exposed to "overpressure" in a lab device called a barochamber. The investigators dial up or down the pressure and control its duration.

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Photo by Laurence Marchionda

Explosive research—Alessandra Leonardi Dal Cengio, MS, checks the settings on the "shock tube" that a VA and Wayne State University team is using to simulate the effects of bomb blasts.

HIGHLIGHTS

VA Research Week spotlights our investigators' achievements

by **Joel Kupersmith, MD**
Chief Research and Development Officer

This year, VA Research Week will take place May 11–17 and will be marked by a variety of events at VA medical centers, ranging from scientific symposia and poster sessions to health fairs, tours and appreciation luncheons for veterans and their families. The purpose is to celebrate the achievements of VA researchers and educate our constituents and stakeholders—as well as the media and general public—about the role of VA research in improving veterans' care and advancing medical science.



In addition to the many Research Week activities taking place nationwide, a special research forum will be held at VA headquarters in Washington, DC, on May 23. The event will feature presentations by some of our leading researchers, as well as remarks from VA Secretary Dr. James Peake and other dignitaries.

Whether you are a member of the VA research community or simply someone with a professional or personal interest in VA research, it is my hope that you will be able to attend and participate in one of our Research Week events. We have an exciting story to tell about how VA research is helping veterans and the whole nation, and we are eager to share it through venues such as these.

Speaking of "telling our story," you will notice that this issue of *VA Research Currents* features a new design. Innovation is one of the hallmarks of VA Research, so we welcome this new and improved look for the newsletter and trust that it will enhance our efforts to keep you abreast of our scientific advances and other important items. —



Coping with the effects of blasts—The pressure wave from roadside bombs and other improvised explosive devices (IEDs) can cause traumatic brain injuries for troops even when they are many feet from the source of the blast and suffer no other physical injuries. The Defense and Veterans Brain Injury Center estimates that from 10 to 20 percent of troops serving in Iraq or Afghanistan have suffered some type of brain injury.

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VandeVord: “If there’s an explosion, there’s a shock wave. But once it gets transmitted to your brain, it’s not a shock wave anymore. It’s a high-speed compression wave. We are generating that compression wave in the barochamber. It simulates what we believe occurs in the brain.”

The goal is to learn how the cells respond to different levels of blast injury. The researchers look at whether cell membranes get damaged, for example, or at what point cells ultimately die.

VandeVord also has funding from the Office of Naval Research (ONR) to conduct animal studies of mild brain injury. Whereas the VA study focuses on cells, the ONR project focuses on tissue. The findings from both will give a fuller picture of the biology of brain injury.

The Defense and Veterans Brain Injury Center estimates that from 10 to 20 percent of troops serving in Iraq or Afghanistan have suffered some type of brain injury. Most of the injuries are considered mild—but even many of these cases will involve permanent cognitive and emotional problems that can tear apart the lives of veterans and their families.

Much of the ONR-funded phase of VandeVord’s work takes place in a large, open space equipped with a 22-foot-long metal shock tube. The back end of the device—the driver—forces a sudden burst of air down a long cylinder, simulating the pressure wave of an explosion. The researchers wear ear protectors and wait in a separate, Plexiglas-enclosed room when the blasts rip through the tube.

Inside the shock tube are brain cells suspended in gelatin, or rats. The blasts range in size from 5 to 20 pounds per square inch (PSI)—small by comparison with typical roadside bombs. But the blasts are

scaled down for testing on rodents. Depending on the duration of exposure, a lethal dose of overpressure for a rat would be around 35 PSI.

“We’re trying only to induce mild brain injury,” says VandeVord. She says using animals is the only way scientists can learn what might be happening in human brains. “We’re at a critical point in the research, and we can’t practice on people. We have to go through these steps and optimize what we can before we can get approval to try something in humans.”

Research may lead to therapies for combat zones

Based on findings from both the VA- and ONR-funded work, VandeVord and colleagues will aim to design therapies that can be administered in the combat zone to troops—either before they go out on patrol, as a preventive measure; or after a blast has occurred, to stem damage to the brain.

According to VandeVord, in more severe injuries, brain cells die and the damage is more likely to be irreversible. In milder brain injuries—including many instances where soldiers or Marines are many feet away from the blast and suffer no visible wounds—cells may not die, but they do get

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damaged. Says VandeVord: “A lot of the guys with mild TBI can recover in six months’ time. What is the point where the cells will die, and what is the point where the cells can still repair themselves?”

Figuring out the relationship between the power and distance of a blast, and the exact effects on brain cells and tissue, is her focus right now.

Studies include genetic component


Some of the lab rats undergo post-blast brain scans using a rodent-sized MRI machine. Others undergo blood tests in which the scientists look for proteins, released by injured cells, that could be biomarkers of brain injury. This may lead to a blood test that military medical personnel could give to troops immediately after a blast to determine if they are physically OK or if there is subtle damage.

“We’re hoping this can translate to the soldiers,” says VandeVord. “If we find something that’s in the blood, it could enable doctors to do a quick test to see how much damage has occurred and then administer therapy accordingly.”

The rats also undergo cognitive testing before and after the blasts. The researchers hope to correlate changes in memory to the level of blast exposure and to specific changes they are seeing in the rodents’ brains.

“We use a maze,” explains VandeVord. “We do several training periods and we see how long it takes the rats to perform a task. Then we test them after the blast to see if it takes them longer.”

Through both the VA-funded cellular work and the ONR-funded animal studies, VandeVord’s team also hopes to learn which genes get activated in brain injury. Figuring out a way to turn off those genes with a drug could spell a breakthrough for the treatment of brain injury on the battlefield and in field hospitals.

“When the brain is exposed to overpressure from a blast, we believe there’s a cascade of negative events that occurs, and this is set in motion by certain genes that get turned on,” says VandeVord. “If we can learn how to stop the expression of those genes with some type of pharmacologic agent, we can stop this cascade of events within the brain and possibly limit the damage.” 

Other TBI research

VA investigators conduct a wide range of studies relating to traumatic brain injury (TBI). Here are examples:

- A team of VA researchers is studying “best practices” in polytrauma care—with a focus on TBI therapy—with the goal of implementing them throughout VA.

- Researchers at VA’s Polytrauma Center in Palo Alto are exploring innovative rehabilitative techniques for brain-injured veterans, including robotic movement therapy and simulated driving assessments.

- The Defense and Veterans Brain Injury Center, a project of VA and the Department of Defense, is investigating drug therapies to treat TBI symptoms such as headaches, anxiety and mood swings.

- VA scientists are exploring the use of gene therapy, cell transplantation, tissue engineering and other cutting-edge strategies to help regenerate nerve cells in TBI as well as conditions such as spinal cord injury, multiple sclerosis and Alzheimer’s disease.



Brain tissue under the microscope—Lead investigator Pamela VandeVord, PhD (at computer), discusses a slide showing rat brain tissue with postdoctoral student Roche de Guzman, PhD (seated), and research assistant Li Mao, MD. The team is studying the biological changes that occur in the brain as a result of overpressure from blasts.

Martin Albert, MD, PhD, director of the Harold Goodglass Aphasia Research Center at the Boston VA Medical Center, was cited in an April 22 *New York Times* article as the developer, in the 1970s, of an innovative approach to stroke rehabilitation called melodic intonation therapy. The *Times* article told how the therapy helped a 62-year-old New York man recover his ability to speak after suffering a stroke five years ago.

David Sheps, MD, MSPH, a research cardiologist at the Gainesville VA Medical Center and the University of Florida, was quoted in an April 22 *U.S. News and World Report* article about his study on stress-induced ischemia. The study, published April 14 in the *Archives of Internal Medicine*, found that heart patients with a certain genetic variation are more likely to experience reduced blood flow to the heart because of mental stress.

Michael Kelley, MD, of the Durham VA and Duke University, has been featured on NBC's "Today Show" along with Duke junior Josh Sommer, who has a rare form of cancer called chordoma and has been working in Kelley's VA lab, one of the leading sites for chordoma research.

Robert Rohwer, PhD, director of the Molecular Neurovirology Lab at the Baltimore VA Medical Center, was quoted in a March 28 *International Herald Tribune* article about a growing trend in the pharmaceutical industry away from animal sources of ingredients for drugs and toward synthetic alternatives.

Thomas Bird, MD, a neurogenetics expert at the Seattle VA Medical Center, was featured in a March 10 *Associated Press* article about his recent study documenting that adults whose parents both have Alzheimer's disease may be at substantially increased risk for the disease. —



Photo by Ed Conlino

Alzheimer's screening—**Mike Weiner, PhD**, director of VA's National Center for the Imaging of Neurological Diseases at the San Francisco VA Medical Center, was quoted in a March 27 article in *The National Post*, a Canadian paper, about the ethics of informing patients about their future risk for Alzheimer's disease based on the results of brain scans or other screening tests.

Career milestones

Charles Robinson, DSc, PE, of the Syracuse VA Medical Center, was named chair-elect of the College of Fellows of the American Institute for Medical and Biological Engineering (AIMBE). Robinson, who has been with the agency for 26 years and was the first VA investigator to hold the title of senior rehabilitation research career scientist, helped found AIMBE in the early 1990s, and has held numerous leadership positions in the bioengineering community.

Richard Frankel, PhD, senior research sociologist at the Roudebush VA Medical Center in Indianapolis, was named along with coauthor Howard Bechman, MD, as a recipient of the Lynn Payer Award from the American Academy on Communication in Healthcare. The team, which has been publishing works on patient-physician communication since the 1980s, was cited for producing "a body of literature that is foundational to the Academy and the work of healthcare professionals."

David Atkins, MD, MPH, is the new director of VA's Quality Enhancement Research Initiative (QUERI) program. Atkins, based at the Office of Research and Development in Washington, DC, was previously chief medical officer at the Center for Outcomes and Evidence at the Agency for Healthcare Research and Quality, where he oversaw that agency's 13 evidence-based practice centers. Atkins is a graduate of Harvard College and Yale University School of Medicine and earned his master's in epidemiology from the University of Washington. —

Studies under way in VA to advance genomic medicine

A review article published in the March 19 *Journal of the American Medical Association (JAMA)* by researchers from VA and the RAND Corporation has focused attention on the burgeoning movement to incorporate genomics—the use of patients’ individual genetic profiles to customize care—into everyday medical practice. VA has a rich array of research projects relating to genomic medicine and expects to be in the forefront of its widening implementation.

The authors of the *JAMA* article, who synthesized findings from 68 studies, found that on the whole, health professionals and the public in the U.S. and other developed countries are unprepared to make effective use of genomics to prevent, diagnose or treat common chronic illnesses such as diabetes or heart disease.

“Primary care clinicians are on the front lines of patient care and they are going to need to be prepared to incorporate genetics into their practices,” said lead author Maren Scheuner, MD, MPH, of RAND. “Training and educating the health care workforce about the role of genetics in their clinical practice and increasing the size of the genetics specialty workforce are potential solutions to the barriers we identified.”

The study was funded by VA to inform its agenda for research on genomic medicine and to help guide the implementation of genomic medicine in its health system. The everyday use of genomic medicine in VA nowadays is still limited in scope, as in U.S. health care in general, but the agency has launched an ambitious research agenda to iron out the ethical, logistical and scientific issues that need to be resolved before the field can expand.



Photo by Jessica Bowen

It’s in the genes—(From foreground) Technicians Weleetka Carter and Angie Stone operate a machine that reads DNA chips in the Pharmacogenomics Analysis Lab at the Little Rock VA.

Laying the groundwork for the expansion of genomic medicine involves thorny ethical issues.

Current policy at VA hospitals and clinics is to provide whatever genetic tests are clinically necessary and appropriate.

“In applying that policy on the clinical side, it means that we normally don’t do any tests that are not related to the diagnosis or treatment of patients,” says Michael Brophy, MS, MT (ASCP), associate chief consultant for VA’s Diagnostic Services office. “While the individual provider makes the decision on what tests to order,

those that provide little if any diagnostic value are generally not ordered in VA.”

An example of a genetic test that *would* be provided is the test to confirm the diagnosis of hemochromatosis, a hereditary condition in which iron builds up in the body. Another example is ApoE genotyping, used to predict a patient’s response to cholesterol-lowering statin drugs or to help diagnose Alzheimer’s disease. VA doctors also commonly use genetic tests to help diagnose breast, colon and other cancers.

Tests whose clinical value is debatable are less likely to be offered in VA, says Brophy. For example, about five percent of patients carry a gene that makes them very sensitive to the blood thinner warfarin, sold as Coumadin. But offering the test appears

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to have little impact on patient care and outcomes. Brophy: “Most of the clinicians just didn’t feel it was going to make much practical difference when looked at from the perspective of real clinical outcomes. Because if you start patients on a low dose as you’re supposed to, and then adjust their therapy upward, the genetic predisposition, when considered along with the other variables, is generally not as relevant. It’s only one of many factors that determine the appropriate dose.”

Next decade may bring dramatic progress

Ron Przygodzki, MD, associate director for genomic medicine with VA’s Office of Research and Development, agrees that the test for warfarin “is a good step forward in the right direction” but not yet a magic bullet for physicians.

Similarly, he points out that much of the predictive DNA testing purchased by veterans and other consumers through various Internet sites offers little practical benefit. He says most of the tests come back with results indicating only a slightly elevated risk for this or that medical condition, based on a combination of single nucleotide polymorphisms—genetic variations—that may or may not be clinically significant. The information is thus unlikely to affect decisions by patients or their doctors.

“The only thing your physician could tell you, for example, is that you may be susceptible to diabetes, or obesity,” says Przygodzki. “There are no bona fide studies to get a real answer on what this really means. Most diseases involve a lot of medical and lifestyle factors. We can’t put a finger on one thing.”

However, he expects the situation to change dramatically over the next decade as researchers in VA and elsewhere continue to refine and expand genetic testing and study how to best use the results to improve care. A case in point: Katherine Meyer-Siegler, PhD, a research chemist at the Bay Pines (Fla.) VA Medical Center, recently found that genetic variations associated with a protein called macrophage migration inhibitory factor may signal an increased risk for prostate cancer recurrence. Findings such as these could eventually make an important difference for patients and doctors deciding on a treatment approach.

Survey of veterans to help guide efforts

Aside from biomedical advances, laying the groundwork for the expansion of genomic medicine involves thorny ethical issues. For example, how are DNA samples stored and for how long? How is the information “de-identified,” and who has access to it? DNA samples collected as part of VA research studies are handled according to strict and clearly defined rules. But if DNA testing

‘We have to protect the veterans we care for and handle their genetic information in a way that’s safe and beneficial for them.’

becomes a much bigger part of routine clinical care, VA will need additional policies governing its use.

Tackling such issues is one of the jobs of VA’s 13-member Genomic Medicine Advisory Committee, which includes genetics experts and representatives from veterans’ groups. The group was formed in 2006 to advise VA on scientific and ethical issues related to the establishment, development and operation of a genomic medicine program.

Additional guidance is expected from an Internet-based survey of about 900 veterans now being conducted for VA by the Genetics and Public Policy Center (GPPC) at Johns Hopkins University. The survey was designed based on results from focus groups held with veterans nationwide over the past year. GPPC recently conducted a similar survey of the general public for the National Human Genome Research Institute.

Sumitra Muralidhar, PhD, a scientific program manager with VA’s Office of Research and Development, says the survey should provide important answers to help guide VA’s eventual implementation of genomic medicine.

According to Muralidhar, “The survey questions generally relate to what aspects of the genomic medicine program veterans are optimistic about, what they are concerned about, and what their expectations are—for example, whether they think the program will benefit their healthcare, whether they would expect compensation for participation, what types of research their genetic information should be used for, who should have access to their samples and data, and what their expectations are with regard to privacy and security of their genetic information.”

Adding genetic data into the electronic health record

Przygodzki notes that VA researchers are also working with outside experts to examine issues such as how to merge genetic information into VA’s innovative electronic health record, which serves as an invaluable tool for VA clinicians and researchers.

As reflected in the VA-RAND study in *JAMA*, adding genetic information to health records is just one of many infrastructure issues that will need to be resolved before genomics can be used more widely in VA. “The technology is coming around,” says Przygodzki, “but we need to create the structures for educating

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Heart hormones may be effective cancer treatment

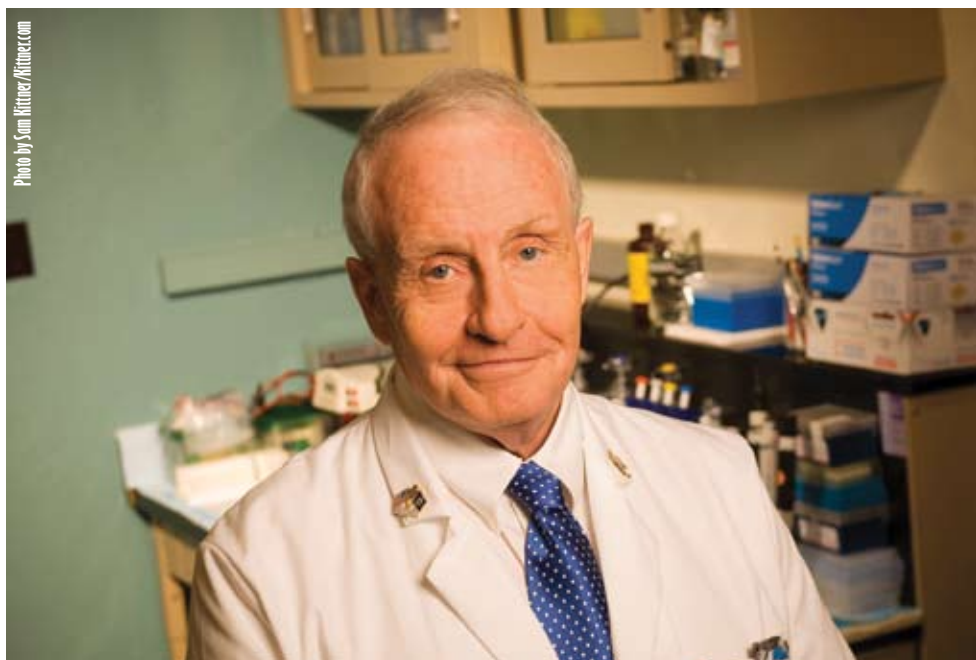
In studies presented by a VA researcher at the Experimental Biology 2008 conference, held April 5–9 in San Diego, hormones produced by the heart eliminated human pancreatic cancer in more than three-quarters of the mice treated with the hormones and eliminated human breast cancer in two-thirds of the mice.

The work was conducted by David Vesely, MD, PhD, chief of endocrinology, diabetes and metabolism at the James A. Haley VA Hospital in Tampa and a professor of medicine, molecular pharmacology and physiology at the University of South Florida.

Vesely has published the work in journals such as *Anticancer Research* and *In Vivo*. The hormone treatments have not yet been tried in humans, but a private biotechnology company is raising money with the goal of beginning human clinical trials.

In the past, scientists and physicians thought the heart was little more than a mechanical pump, delivering blood and oxygen to the body. But that view changed dramatically in 1981 with the discovery that the heart produces a protein called atrial natriuretic factor (ANF), so-named because it is made in the atrium of the heart and triggers the production of urine and the excretion of sodium.

Vesely later discovered three more hormones that are produced from the same gene as ANF: long acting natriuretic peptide, which also stimulates urine production and sodium excretion; vessel dilator, which opens the blood vessels and lowers blood pressure; and kaliuretic peptide, which increases potassium excretion.



Cancer fighter—David Vesely, MD, PhD, studies cardiac hormones with anti-tumor properties.

The lab results were especially promising in regard to pancreatic cancer.

Vesely began his research on cardiac hormones by looking at the role they can play in diagnosing and treating congestive heart failure. But following his wife's death from breast cancer in 2002—and in response to increasing evidence that the hormones controlled cell growth—he decided to test the effects of the hormones in cancer cell cultures.

Using colon, ovarian, breast, prostate and pancreatic cancer cells, among others, Vesely found that the hormones kill up to 97 percent of all cancers in cell cultures within 24 hours. He then turned to trials with mice, injecting some with pancreatic cancer cells and others with breast cancer cells. Once the mice developed tumors, he treated them with the hormones.

At the end of one month, the treatment had eliminated cancer in 80 percent of the mice injected with human pancreatic cancer and in 66 percent of the mice injected with breast cancer.

The results with pancreatic cancer were particularly exciting because it is a fast-growing cancer with a poor prognosis. The disease responds poorly to chemotherapy and radiation, and surgical removal of the pancreas is risky. As a result, patients rarely survive past five years. In Vesely's study, the pancreatic cancers that were not cured were reduced to less than 10 percent of their original size.

“Significantly, even in the carcinomas that [the treatment] didn't cure, it decreased the volume of these cancers to less than 10 percent, and the animals didn't die of cancer—they died of old age,” says Vesely. “Thus, this is a new concept in cancer treatment. Even if you don't cure every cancer, some can be treated like a ‘chronic disease’ that one lives with but doesn't die from.”

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patients, physicians, and caregivers. We also need to make sure that we put the information into the medical file so clinicians and researchers can use it appropriately and effectively.”

First and foremost, he says, “We have to protect the veterans we care for and handle their genetic information in a way that’s safe and beneficial for them.”

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Vesely also suggests that the hormones would be a nontoxic treatment, unlike conventional chemotherapy. “Since these peptides are made by your own body, they have almost no side effects. The body doesn’t recognize them as foreign, and thus, it doesn’t develop antibodies which can affect a person’s immune system.”

In Vesely’s studies with mice, the hormones did not appear to cause any of the unwanted side effects associated with most cancer drugs now in use. He says, “In the lab, we gave these peptide hormones 24 hours a day for an entire month at the concentration which eliminates cancers growing in living tissue, without a single side effect.”

INVESTIGATOR SNAPSHOT



Photo by Michael Moody

Caring for a diverse population—Somnath Saha, MD, MPH, is a staff physician at the Portland VA Medical Center and an associate professor at Oregon Health and Science University. He has been funded by VA, the National Institutes of Health and the Robert Wood Johnson Foundation to study the role of racial barriers in patient-physician relationships, the extent to which these barriers explain health care disparities, and the role of physicians’ “cultural competence” in mitigating these barriers.

Says Saha, “VA researchers have made substantial contributions to disparities research and in many areas have led the way. This is because VA is an ideal place to study racial disparities, because of the minimization of financial access barriers and because of our information systems and diverse population. Some of the most noteworthy studies in the disparities literature have come from VA. It is also because VA has prioritized research on disparities, with the goal of reducing and eliminating them.”