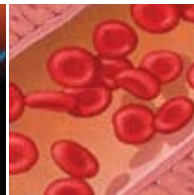
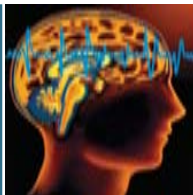


VA RESEARCH CURRENTS



NEWS FOR THE RESEARCH COMMUNITY OF THE U.S. DEPARTMENT OF VETERANS AFFAIRS • FEBRUARY 2007



Henry Diaz, an Army veteran who lost his leg in a civilian auto accident, demonstrates the stair-handling ability of the microprocessor-controlled Rheo Knee, as Dr. Robert Gailey looks on.

Evidence-based prosthetics is focus of new workshops

Robert Gailey, PhD, PT, is happy to see his research career going “backwards.”

A physical therapist and investigator at the Miami VA Medical Center and University of Miami, Gailey has been funded by VA to study the best ways to identify the functional deficits of amputees. He hopes to enroll 90 veterans, most with amputations resulting from diabetes-related vascular disease.

“This is one of the first times we’ve done something ‘in reverse,’ explains Gailey. “My career has been based on working with Paralympic athletes and high-functioning amputees, develop-

ing training programs for them, and then introducing those exercises to the elderly. We’ve had tremendous success and raised the bar of expectation for the dysvascular amputee. Now, what we’re doing is just the reverse: We’re learning from the dysvascular amputee how to identify what needs to be done, and the next step is to translate that for the traumatic and younger amputee.”

Gailey’s research is one of the driving forces behind a new series of workshops his team is holding for prosthetists and physical therapists throughout VA. With

see **PROSTHETICS** on pg. 4

Message from the CRADO

New certification process will boost data security

By Joel Kupersmith, MD, chief research and development officer

Despite much hard work by researchers and others in VA to comply with existing guidelines and regulations regarding data security, recent events in VA and at other institutions caution us that we need to do even more in this area.

As part of our increasing focus on this critical issue, we notified the field on Feb. 6—through an email and two special conference calls—of a set of new initiatives designed to upgrade and tighten our data-security procedures. These initiatives, developed in concert with VA’s offices of Research Oversight and Information Technology, are described in full detail on the VA research website at www.research.va.gov. Simply click on the large “Protecting VA Research Information” button on the homepage.

In a nutshell, these procedures center on a new annual training requirement and a careful review of all existing research projects. The review will entail an annual

see **SECURITY** on pg. 2



Deployment health proposals sought

ORD continues to seek innovative proposals focused on improving the health of veterans returning from operations Iraqi Freedom and Enduring Freedom. Proposals may be submitted through fiscal year 2008 to any of ORD’s four research services, in accord with regular Merit Review application timelines.

Studies to be funded under this initiative may address, for example, topics such as polytrauma, neurotrauma, burns, pain, posttraumatic stress disorder, or other aspects of OIF/OEF veterans’ physical, cognitive and psychosocial recovery. Full details are available on the VA research website: www.research.va.gov.

Career milestones

Cynthia Brown, MD, Birmingham, will be one of 10 researchers to receive a New Investigator Award from Merck and the American Geriatrics Society at the group's annual meeting in May. Brown, a VA RR&D Career Development awardee and medical director of her site's Geriatric Research, Education and Clinical Center (GRECC) Fall Prevention program, is studying ways to measure mobility during hospitalization.

Mary J. Eaton, PhD, a neurobiologist with VA and the Miami Project to Cure Paralysis, was selected as Eminent Scientist of the Year in 2005 (to be awarded this year) for her lab studies of cell therapy to treat chronic pain in spinal cord injury.

Vibha Bhatnagar, MD, MPH, a clinical epidemiologist at the San Diego VA, won the 2006 AstraZeneca Scholarship Award from Nature Publishing Group for his paper "Estimating the Risk of Long-Term Erectile, Urinary and Bowel Symptoms Resulting from Prostate Cancer Treatment," which appeared in *Prostate Cancer and Prostatic Diseases*.

Roger K. Long, MD, PhD, San Francisco, won a National Space Biomedical Research Institute postdoctoral fellowship to support his studies on bone loss associated with space flight. His mentor is Daniel Bikle, MD, PhD.

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SECURITY (from pg. 1)

certification process involving principal investigators with active projects, associate chiefs of staff for research and development, medical center directors, VISN directors, and VISN support teams. PIs will need to certify on a project-by-project basis that the use, storage and security of all research information connected with the project will be in compliance with all VA and VHA requirements. The goal is to ensure that each VA facility that performs research has appropriate data-security and privacy policies and procedures in place, and that these policies and procedures are being followed.

Due dates for the first stages of the new procedures are fast approaching, especially for staff at HSR&D REAPs, who are being asked to take certain extra measures. So please make it a top priority to educate yourself on this urgent and most important issue. Complete details and all supporting documents can be found on the website.

Once you have accessed the information on the website, further questions can be sent to the following dedicated email address: Researchdata@va.gov. Responses to frequently asked questions (FAQs) will be posted on the website as this material develops. Finally, we plan to hold conference calls at least every two weeks during the coming months to provide further opportunities for questions and discussion concerning this initiative.

As Secretary Nicholson has pointed out, establishing a culture that eliminates all risk of data theft or loss is a complex and difficult task. Nonetheless, it is a challenge that must be met—otherwise, we will not be able to continue our vital work as VA researchers. If we persevere and work diligently together, we can ensure the highest level of security possible and honor the trust placed in us by the nation and the veterans we serve. ■

Methodology moments

Observational study designs:
The cohort study

This bimonthly feature, prepared by VA's Seattle Epidemiologic Research and Information Center, addresses topics in research methodology that are of broad interest to Research Currents readers. References and links are provided on the Seattle ERIC's website at www.eric.seattle.med.va.gov/research_currents.html.

Imagine that a new drug, mungafenil, has become widely used for erectile dysfunction (ED). A VA clinical researcher suspects that mungafenil may sometimes precipitate atrial fibrillation (AF). How could this suspicion be formally tested?

In principle, a *randomized trial* would yield the most definitive answer, comparing AF incidence between ED patients assigned at random to receive mungafenil or not. But often it may be impossible, impractical, or unethical to manipulate patients' exposure to a drug or other agent for research purposes. Instead, an *observational study* may be the next best alternative. Here investigators would not try to influence anyone's use of mungafenil. Instead, they would merely examine the association between mungafenil use and AF among ED patients in routine care.

Among various observational study designs, a *cohort study* most closely resembles a randomized trial. It involves first identifying two groups of patients: one group of mungafenil users (the *exposed* group), and a comparison group of mungafenil non-users (the *unexposed* group). These groups might, for example, be identified through medical records or pharmacy data. Then the frequency of AF

Study suggests controlling iron levels early in life may cut future heart risk

A six-year study by VA researchers suggests that reducing the body's excess iron stores—in this case, by drawing blood—may improve clinical outcomes for people with symptomatic but stable peripheral arterial disease (PAD), but only if iron reduction begins at a relatively young age. The findings appeared in the Feb. 14 *Journal of the American Medical Association*.

“While our study did not show that reducing iron led to across-the-board decreases in overall mortality, or combined death plus non-fatal myocardial infarction and stroke, it did support the theory that vascular health might be preserved into later life by maintaining low levels of iron over time,” said lead author Leo R. Zacharski, MD, a physician-researcher at the White River Junction (Vt.) VA Medical Center and Dartmouth Medical School.

Iron linked to heart health

Excess iron in the blood is thought to promote free-radical damage to arteries, particularly in the early stages of atherosclerosis, a major risk factor for heart attack and stroke. Researchers posited in the 1980s that premenopausal women have lower cardiovascular risk than men because they regularly lose blood—and excess iron—through menstruation. At least two large studies in the late 1990s seemed to support this notion: They found that men who donated blood—and thereby lowered their iron levels—had fewer cardiac problems than men who didn't donate. But other studies have yielded mixed results, and the topic is still debated among doctors.

The new trial, funded by VA's Cooperative Studies Program, involved 1,277 men and postmenopausal women with PAD, ages 43 to 87, at 24 VA medical centers. Patients were randomly assigned to no iron reduction or iron reduction by phlebotomy,



Photo by Allen Kaufman

A study led by Leo Zacharski, MD (foreground), found that reducing blood iron levels through phlebotomy had a beneficial effect on all-cause mortality and other outcomes in a subset of younger patients, those ages 43 to 61.

with removal of defined volumes of blood at six-month intervals. The volumes of blood draws were calculated to avoid iron deficiency.

Phlebotomy was used, said Zacharski, because it is “safe and inexpensive, and correlates to routine blood donation, an ‘over-the-counter’ procedure that appears to contribute to improved vascular health.” He emphasized, though, that pending further research, people should not seek to donate blood simply to lower their iron levels, and that similar effects could be achieved through dietary restrictions or drug treatment.

Younger patients show benefit

Over more than three years of follow-up, on average, there were 125 deaths from any cause in the iron-reduction group, versus 148 in the control group. In terms

of the secondary outcome measure—death from any cause, or nonfatal heart attack or stroke—there were 180 events in the iron-reduction group and 205 in the control group. In neither case was the difference significant. But when Zacharski's team analyzed the results for pre-defined subgroups, they found that among younger patients—those ages 43 to 61—there were 54-percent fewer deaths from all causes in the iron-reduction group, and 57-percent fewer deaths plus nonfatal heart attacks and strokes.

Said Zacharski, “We suspect that the toxic effect of excess ferritin may become permanent at an older age, such that the benefits of iron reduction are realized only if it is started early and continued over time.” He said more research is needed to better define the relationship between iron and cardiovascular disease and determine how best to counter what are conclusively shown to be harmful effects of iron. ■

PROSTHETICS (from pg. 1)

support from the prosthetics manufacturer Ossur, the first event was held in Miami from Jan. 16 – 18. Others will follow, in different regions. The goals are to acquaint VA clinicians with the latest bionic technology, guide them in developing training programs for amputees who use the equipment, and promote a seamless transition between Department of Defense and VA rehabilitation programs.

“We want to bring VA practitioners up to speed on the latest technology that soldiers are receiving in the military rehabilitation facilities,” says Gailey.

VA ‘paving the way’ with clinical trials

Another phase of research by Gailey’s group and others within VA is studying the differences among the new prosthetic limbs, and determining how to best match them with veterans’ needs. For example, the Rheo Knee from Ossur and C-Leg from

Otto Bock both feature high-end microprocessors. But the Rheo, with a faster microprocessor, offers more “swing control” to enable users to walk faster, while the C-Leg is known for having more “stance control” and may be better for someone with poor balance who needs more stability.

Clinical trials comparing prosthetic limbs have been difficult because of a lack of well-established outcomes measures, says Gailey. But studies such as his new one, aimed at better identifying amputees’ functional needs, are part of a larger effort within VA to generate hard evidence to guide care and prosthetics fitting.

“This is where VA is paving the way,” he notes. “Our study, ‘Evidence-Based Amputee Rehabilitation,’ is among the first where a functional measure is being used in the clinic to look at balance, power, strength and other outcomes. We then will try to elevate the patient’s function—not by ‘shot-gunning’ treatment, but by targeting specific elements or functional limitations and then giving appropriate therapy.”

‘Almost every socket design and component can trace its foundation to VA research.’

While his new project will include mainly diabetic amputees, most of whom are older and less active, he expects the research to also benefit returning OIF/OEF veterans.

“We wanted to focus on the majority, not the minority. We’re trying to take care of the largest amputee population within the VA. But the principles of using a clinical assessment tool and then putting together an individualized program based on the results is something we can translate to the younger, traumatic amputee population. In fact, we now have a different set of items, of higher difficulty, for this group.” He hopes to work with DoD colleagues in the future to develop a standardized measurement instrument targeted to younger, stronger, more active amputees.

Strong partnership between VA and Department of Defense

Gailey says collaboration between VA and DoD in prosthetics is robust. Paul Pasquina, MD, medical director of amputee care at Walter Reed Army Medical Center, was on the faculty at the Miami VA workshop—one of many recent examples of clinicians from the two agencies participating in workshops together. And VA physical therapists and prosthetists will have residencies at the Center for the Intrepid, the Army’s brand new \$50 million facility at Ft. Sam, Texas, for the care of servicemen and women with wounds such as limb loss and burns.



Brad Holling, a Special Forces Ranger who lost his leg when his Blackhawk helicopter went down in Somalia, wears a Power Knee. Part of the system is the transponder on his right leg, which monitors the natural leg’s movement and signals the artificial knee to behave similarly.

Photo by Larry Glisard

COHORT (from pg. 2)

would be monitored and compared between groups over a defined time period, possibly through medical-record surveillance.

A cohort study could be either *prospective* or *retrospective*:

- In a *prospective* cohort study, the AF episodes of interest would occur in the future relative to when the study is initiated. This option lets the researcher collect additional data concurrently for research purposes that may not be captured in medical records.

- In a *retrospective* cohort study, the AF episodes of interest would already have occurred before the study actually got under way. Pre-existing medical record data would be used to "reconstruct" a comparison between users and non-users over a follow-up period already past. When sufficiently complete and detailed archival data permit this option, it can yield an answer relatively quickly and efficiently.

A key concern in any observational study is the possibility of *confounding*. Without randomization to balance the groups, mungafenil users may differ from non-users in ways that also influence their risk of developing AF—for example, pre-existing heart disease. If so, the observed mungafenil-AF association could be distorted, mixing a possible true effect of mungafenil with spurious differences due to the confounding factors. To avoid bias, the researcher would need to identify, measure, and control for relevant confounding factors using techniques discussed later in this series. ■

Next ORD field conference call:

Monday, Feb. 26, 2007 • 1:30 pm EST

Dial 1-800-767-1750
(access code: 17323)



Mike Meinen, a retired Army sergeant who lost his leg when a rocket-propelled grenade shot through his Humvee in Iraq in 2003, demonstrates the Power Knee. With him are Ian Fothergill, CPO, of Ossur and members of a local Fox News film crew who covered the event at the Miami VAMC.

PROSTHETICS (from pg. 4)

While DoD may be on the front lines of clinical care for returning veterans, at least in their early stages of rehabilitation, Gailey says VA is playing a critical leadership role in prosthetics education and research.

"Many of the prosthetic developments since World War II have come from the VA," he says. "If you look at it historically, almost every socket design and almost every component can trace its foundation back to VA research. We're recapturing that leadership role once again, because it's necessary." ■

Salt Lake City research to target prosthetic infections

Researchers at the Salt Lake City VA and University of Utah, led by Roy D. Bloebaum, PhD, are testing whether a promising new antimicrobial wound dressing can reduce the risk of infection in osseointegration. A surgical technique developed in Sweden but not yet in wide use, osseointegration allows for prosthetic legs to be attached to the body via a titanium bolt implanted directly in the residual bone. The product being tested was developed at Brigham Young University and is licensed to Ceragenix Pharmaceuticals.

The rich history of VA research

The birth of nuclear medicine in VA

The following account is based on an excerpt from “VA Research, 1925 – 1980,” a history compiled by Dr. Marguerite Hays, who directed VA’s Medical Research Service from 1974 – 1979 and the overall VA research program from 1979 – 1981. The complete, fully referenced text is expected to be available in print or on CD later this year. The material below has been edited slightly due to the space constraints of this newsletter.

One VA research area that took off quickly after World War II was research in the use of radioisotopes. General Paul Hawley, the Chief Medical Director, had become deeply concerned about the problems that the possibility of nuclear warfare might create for the VA. He held a conference in August 1947 with key VA and military health officials, including officers who had worked on the Manhattan Engineering Project. Among them was Dr. George Marshall Lyon, who had been assigned to the project as a naval officer and was the ranking medical officer at the Bikini tests in the Pacific. He was recruited in 1947 as “Special Assistant to the Chief Medical Director for Atomic Medicine.” His charge was to prepare the VA to handle claims for injuries associated with the atomic-bomb tests.

VA leads civil preparedness against atomic attack

Few if any such claims were ever received, but the Atomic Medicine unit kept up with the literature on radiation



Herbert Allen, MD, manually scans the radioactivity in a patient’s thyroid gland.

effects. Soon, under Lyon’s leadership, the VA set up a Radioisotope Section of the Research and Education Service, with Lyon as its chief. Lyon characterized the existence of the “Atomic Medicine” program as a secret, with emphasis on radioisotope research applications in the VA serving to divert interest from the nuclear warfare theme. The VA became the lead agency for civil preparedness against an atomic attack, and staff of the radioisotope units in the hospitals were responsible for civil preparedness at the local level.

Lyon used his personal contacts extensively in establishing the new VA radioisotope program. He quickly proceeded to set up radioisotope departments in as many VA hospitals as possible. At each of them, there was a physician chief and a radiation safety officer, generally a physicist with training in nuclear physics. These VA radiation physicists held courses for other VA staff and for their communities on atomic preparedness and taught local police and fire departments how to handle Geiger counters.

The physicians and scientists in these new VA radioisotope departments began

to explore the uses of radioisotopes for diagnosis and treatment.

In 1947, the Chief Medical Director established a Central Advisory Committee on Radiobiology and Radioisotopes, which helped establish VA radioisotope laboratories in different geographic areas. By the end of 1946, sites for six radioisotope laboratories had been identified, primarily based on the presence of staff and consultants who had been involved in the Manhattan Project. By 1949, 12 radioisotope laboratories were functioning. By 1960, 60 such laboratories had been established. In time, these numbers grew so that every VA medical center with an acute-care responsibility provided nuclear medicine services.

1950s cooperative study tests thyroid therapy

In 1950, Joseph Ross, MD, at the Framingham VA Hospital, together with Herbert Allen, MD, from Houston, Reginald A. Shipley, MD, from Cleveland, and Leslie Zieve, MD, from Minneapolis, formed a group to plan a Cooperative Study of Radioiodine Therapy of Hyperthyroidism. Its goals were to determine the relation between dose and the outcome of treatment, and to search for characteristics that might predict a patient’s response to treatment.

The group also proposed to follow patients over the long term to identify any adverse effects of the treatment, especially the development of thyroid cancer.

see **NUCLEAR** on pg. 8

Health Affairs paper analyzes role of electronic health record in VA diabetes care

After Hurricane Katrina slammed into the Gulf Coast in August 2005, thousands of people found themselves seeking medical care, but without access to their health records. Their charts had become lost, ruined or otherwise inaccessible as a result of the storm. One group not affected in this way, however, were VA patients: VA providers at any other site nationwide could instantly pull up their electronic health records.

The disaster showed the value of an integrated, nationwide, paperless system that allows patients to receive care seamlessly across different locations. But the benefits of VA's system extend further: Clinicians, administrators and investigators in VA are able to use the records—with appropriate security and confidentiality measures in place—to improve care and performance and conduct valuable research.

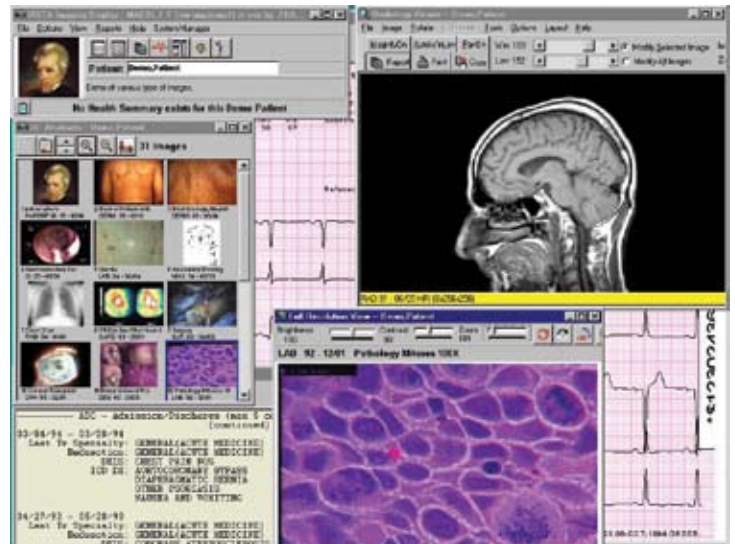
A new article, available online in the current issue of the policy journal *Health Affairs* (www.healthaffairs.org), takes an expansive and insightful look at the history, growth and functionality of VA's electronic record system, and the reasons for its effectiveness. The paper focuses on how the system has enhanced diabetes care—an area in which VA has surpassed the private sector, according to recent studies, and which is especially critical to VA's mission, in that as many as 1 in 4 veterans are affected.

Lead author Joel Kupersmith, MD, chief research and development officer for VA, says VA's metamorphosis since the late 1990s into a top-notch healthcare provider has been enabled by the meld-

'CPRS makes it easier to look at the same group of patients over many years. ...You get a better look at quality of care and outcomes.'

ing of VA's culture, with its emphasis on quality improvement, with the information-rich electronic record system.

"There's been a lot published about the quality of care that VA has achieved, and it's due to a complex of factors," he noted in an interview. "There was a transformation in VA whereby patient indices were followed, performance measures were instituted, and a number of other features were enacted—all of which, when combined with the electronic health record, served to improve quality."



This mock screen illustrates the diversity of the information available to VA clinicians through VA's electronic health record system.

VA's electronic chart system is often referred to as the Computerized Patient Record System, or CPRS. Actually, CPRS is a Windows interface to the umbrella system known as VISTA (Veterans Health Information Systems and Technology Architecture), which contains more than 100 clinical, financial and administrative programs. Through CPRS, providers can securely access patient information in the hospital, clinic, or other points of care. They can update a patient's history, place orders, review test results, and view X-rays and other images. As of Dec. 2005, VISTA contained 779 million clinical documents and 425 million images. Each day, the system is fed another 577,000 clinical documents, 900,000 orders and 600,000 images.

Kupersmith, who on Jan. 26 discussed his paper at a Washington, DC, media symposium on health information technology, sponsored by *Health Affairs*, cited an example of how the electronic health record is a boon to research:

"When we do quality and other health-services research, we may look at a cross section of patients at one point in time, and then look at another cross section six months or a year later. CPRS makes it much easier to look at the same group of patients over many years. So you get around some of the pitfalls in this type of research. You get a better look at quality of care and outcomes. It opens up many possibilities."

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NUCLEAR (from pg. 6)

This study, performed on a purely voluntary basis with little urging from Central Office, succeeded in collecting an early body of data, but it failed to reach a definitive conclusion. Nevertheless, it led to research within the VA to improve the thyroid dose estimate for radioiodine and set the pace for an extensive, more definitive NIH-funded study to address these questions in the late 1950s.

While the radioisotope laboratories increasingly concentrated on providing the latest in patient care, they remained at the forefront of nuclear medicine research.

At the Wadsworth VA Hospital in Los Angeles in the late 1940s, Herbert Allen developed a method to map the radioactivity in the thyroid gland by using a directional probe at many points along a grid over the neck. The technique gave crude imaging information, but it took several hours to complete a study. Allen challenged Dr. Benedict Cassen, a physicist at UCLA, to develop an electrically driven scanner. The result was the first nuclear medicine scanner, developed in 1950 by Drs. Cassen, Allen and William E. Goodwin and used to study the thyroids of patients at Wadsworth. This was the beginning of the imaging of radioisotope distribution in intact persons, a technique that has revolutionized the diagnostic and therapeutic approaches to many diseases and played a key role in improving patient care. ■

ELECTRONIC (from pg. 7)

The *Health Affairs* article details several diabetes-specific benefits of CPRS: For example, the system allows for earlier identification of kidney disease, a major complication of diabetes, and helps identify patients at high risk for amputation, another serious complication. And thanks to more recent enhancements to CPRS, VA has begun implementing teleretinal imaging nationwide to help veterans at risk for, or receiving treatment for, diabetes-related eye disease.

Kupersmith also stressed the importance of another emerging CPRS feature: My HealthVet. This Web-based extension of the system allows registered veterans to obtain electronic copies of key parts of their health records and track personal metrics such as blood pressure and blood sugar, among many other functions. The feature is now being piloted with patients enrolled at nine VA sites.

Said Kupersmith, “This is really the beginning of personalized, patient-centered healthcare.”

Collaborating with Kupersmith on the *Health Affairs* paper were Joseph Francis, MD, deputy chief research and development officer; Eve Kerr, MD, MPH, Sarah Krein, PhD, RN, and Leonard Pogach, MD, MBA, of VA’s Diabetes QUERI; Robert M. Kolodner, MD, VA’s chief medical information officer; and Jonathan B. Perlin, MD, PhD, MSHA, chief medical officer and senior vice president for quality at Hospital Corporation of America and former VA under secretary for health. ■

VA Research Week 2007: May 13 – 19