APRIL 2009

VA Research Currents

RESEARCH NEWS FROM THE U.S. DEPT. OF VETERANS AFFAIRS

Defining the role of race in health research

Eight years ago, when the *New England Journal of Medicine* published two studies comparing the effects of drugs between black and white patients, a debate ensued on the journal's editorial pages and later in the media.

Some experts said race has no place in medical research. One editorialist in the journal said that "attributing differences in a biological end point [in this case, the reaction to a drug] to race is not only imprecise, but also of no proven value in treating an individual patient."

Others said making racial distinctions in this context was justified and even valuable. A *NEJM* editorialist in this camp held that addressing the effects of race on the response to drugs will "be of great help to physicians in their attempt to choose the best therapy for … patients of different races."

The debate is by no means settled, but researchers have continued to refine the way they think about race and ethnicity in

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Caring for diverse populations—Dr. Leonard Egede is a staff physician and disparities researcher at the Charleston VA Medical Center and Medical University of South Carolina.

HIGHLIGHTS

Research Week 2009: 'Turning Hope into Reality'

By Joel Kupersmith, MD
Chief Research and Development Officer

"Turning Hope into Reality," the theme of VA Research Week 2009, underscores the improvements to the lives of Veterans and other Americans that result from VA's research findings.

During the week of May 3 through May 9, with kickoff events April 29 through May 1, VA will recognize the advances that continue to make our program a model for bench-to-bedside research and that lay the foundation for VA's patient care, recognized by many authorities as among the best in the world. In addition to recognizing the achievements of VA researchers, Research Week pays tribute to Veterans who participate in studies, without whom VA's far-reaching research accomplishments would not be possible.

Research Week opening events will take place in Washington, DC. Presentations will address areas such as prosthetics, genomics, mental health care and comparative effectiveness research. For details, visit *www.research.va.gov/researchweek*.

Along with the activities in the nation's capital, VA sites nationwide will be holding their own Research Week events, ranging from scientific presentations to tours, luncheons and exhibits for Veterans and the general public. I encourage you to participate in the events in your area and look forward to seeing those of you who will be joining us in Washington.

Editor's note: Dr. Kupersmith has been named to the new Federal Coordinating Council for Comparative Effectiveness Research. The 15-member council, under the auspices of the Department of Health and Human Services, will oversee comparative effectiveness research funded through the American Recovery and Reinvestment Act of 2009.

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health and health care. For a perspective on the issue, *Research Currents* spoke with Leonard Egede, MD, MS, a physician-researcher at the Ralph H. Johnson VA Medical Center in Charleston, S.C. Egede directs VA's Center for Disease Prevention and Health Interventions for Diverse Populations. He is also an associate professor at the Medical University of South Carolina and directs the school's Center for Health Disparities Research.

Q: When we discuss "race" in the context of health research, are we talking about actual biological differences among people or about social and cultural differences?

A: It depends on the nature of the research. In terms of disparities research, my approach, and what the literature is beginning to suggest, is that race is really a social construct. A lot of what we deal with has little to do with the genetics of race. It's really an issue of the culture you belong to and how you identify yourself. Even if you're multiracial, if you identify as being black, or Hispanic, or a Pacific Islander, that will determine to a large extent the interactions you have, the behaviors you pick up, your value system, your views on life. In fact, most researchers take race and ethnicity and blend them together. Ethnicity is even more of a social construct than race is.

'A lot of what we deal with has little to do with the genetics of race.'

—Dr. Leonard Egede, Center for Disease Prevention and Health Interventions for Diverse Populations

Q: Some racial or ethnic groups are at higher risk for certain diseases. So does this have more to do with race per se or with cultural factors such as diet, lifestyle and socioeconomic status?

A: If we look at diabetes as an example, we see it's a mixture. Diabetes is a polygenic disease, so you have multiple genes involved, but the genes are defined by your environment. So there's some genetic basis for type 2 diabetes, but it's not just genes; it's also the environment. Behaviors and environment are just as important as the genes.

Q: What have we learned about how the biological and cultural factors associated with race or ethnicity interact?

A: I recently gave grand rounds where I spoke on how the environment uncovers latent genetic predisposition to diabetes in ethnic minority groups. Multiple studies show that the longer people stay in America, the more likely they are to gain weight and become physically inactive, and the more their risk of diabetes increases. Several studies have compared Japanese immigrants to the U.S. with those who stayed in Japan. Over time, the risk of diabetes among those who immigrated to America increased two to threefold across the different studies. So here you have people with a similar genetic makeup, but the environment has clearly impacted their risk for disease. I coauthored a paper that looked at the length of residence in America and the risk of cardiovascular disease. In general, we found that among immigrants from diverse ethnic backgrounds, when they've been here for 15 years, the risk of being obese, having high cholesterol and smoking increases dramatically.

Q: What is it about life in America that accounts for these health changes among these immigrants?

A: You have to give credit to this country. It's a great nation with lots of opportunities. It provides lifestyle options that may not be readily available in other countries. As it happens, some of the things that make life pleasurable and enjoyable also increase the risk of disease.

Q: VA and other health systems are increasingly focusing on genomic medicine, which uses patients' genetic information to individualize their care. Is this likely to result in better care for minority patients?

A: In terms of pharmacogenomics—tailoring drugs based on specific genes or genetic responses—I think we'll start seeing more and more of these studies, but I doubt they'll be primarily along racial lines. It may be that certain genes are more prevalent in certain ethnic groups, so you could have certain drugs being targeted more to those groups. But from an economic standpoint, the pharmaceutical industry will have little incentive to make drugs that target only certain groups. More importantly, it appears there are few diseases where you really have a unique response by race.

Q: There's a lot of talk now about comparative effectiveness research—

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large studies that compare different medical treatments for a particular condition. Are these types of studies—which VA has been doing for years—likely to benefit minority groups along with the general population?

A: There have to be large enough numbers of minorities in these trials. That's when you can begin to see how different groups benefit differently from a particular treatment. And you can start to think about how to tailor the intervention to meet the needs of unique groups. That's an important area we need to pursue in terms of outcomes research. Generally speaking, however, to date there hasn't been enough diversity in the populations included in most of these trials. What we need is to involve more minorities in research so we have big enough sample sizes to be able to stratify by race and look at racial differences in outcomes.

Q: Hasn't VA done a fair amount of research specifically looking at how interventions benefit different racial groups?

A: That's true. Some of us are already doing studies where we design an intervention, and our primary aim is to test whether the intervention works at all. Then we have a secondary hypothesis to test whether the intervention works differently between whites and blacks, for example, or between whites and Hispanics. Some of this research is already ongoing, and people are only going to do more and more of it. We've begun to recognize that racial groups do respond differently to many interventions, and maybe these interventions need to be tailored to specific groups.

Q: Why are minorities still underrepresented in health research in the U.S. in general?

Reaching out to rural minorities—Albert Dean, a patient at the Charleston VA, is taking part in a study led by Dr. Leonard Egede that will compare psychotherapy for depression delivered by videophone with in-person care. The study will include more than 200 Veterans, most of them African American, from rural areas in the South.

A: This is partly the result of location. In most parts of the countries, you may end up having two, maybe five percent minority representation. With a lot of the drug studies, they don't have enough minority groups and they don't have a formal hypothesis to test differences across groups. Overall, we're behind. VA and the National Institutes of Health have done a lot in trying to increase diversity in the pool by requiring applicants to state how they're going to address gender and ethnic diversity, but we need to do more.

Q: What else can be done to increase minority representation in research?

A: One answer is something we do a lot of in VA—partnering with other sites where you can have a larger pool of minorities. The push now should be toward doing more multisite studies. They're more expensive, but you end up having data that are more generalizable to the whole population, including minorities. It also helps to have a more diverse workforce. This starts with the investigator. Minority investigators are more likely to be interested in doing research about minorities, and I believe they have a better chance of recruiting from minority populations. I can tell you anecdotally from some of my studies that I'm actually able to recruit more African Americans than whites or Hispanics. This extends to other study personnel as well. When people are being recruited by people of similar ethnicity, they are more inclined to want to participate. The concerns that may stem from the distrust of the past are minimized.

VA investigator feted by Hispanic medical group

Sylvia E. Rosas, MD, MSCE, an investigator with VA's Center for Health Equity Research and Promotion, received the Leadership Fellow of the Year award from the National Hispanic Medical Association at the group's annual meeting in New York on March 21. The award recognized Rosas' leadership on issues affecting the health of the Hispanic community. Rosas is also a staff physician at the Philadelphia VA Medical Center and assistant professor of medicine at the University of Pennsylvania. Her research focuses on cardiovascular disease in patients with chronic kidney disease.

Depression and heart disease: What's the link?

Mitchell Finkel, MD, a cardiologist at the Clarksburg VA in West Virginia, likes to point out that the word "heart" appears more than 700 times in the Bible, "mostly in the context of your emotions."

Indeed, people over the ages have viewed the heart as the seat of the emotions. The link is entrenched in our language: Those who are grieving have a "broken heart." The "heart sings" in those who are happy. Is the connection merely figurative, poetic? Or is there a biological basis for the metaphor?

Researchers have found, in study after study over decades, an undeniable link between emotional illness—namely depression—and heart disease. Not only is depression common among those with heart disease—in fact, it puts patients at greater risk for dying—but it also appears to play a role in causing heart disease in the first place.

"There are some studies going back 50 years demonstrating that depression leads to heart disease," notes Jeffrey Scherrer, PhD, a psychiatry researcher at the St. Louis VA and Washington University. He was lead author on a recent study of more than 1,200 male twins who served in the military during the Vietnam era. Men who reported depression when they were surveyed in 1992 were twice as likely to develop heart disease in the ensuing years. Even among twins, who share similar or identical genetic vulnerabilities to disease, only those who experienced depression were at greater cardiovascular risk.

But how exactly does depression increase heart risk? One school of thought is that depression is a marker for certain behaviors that harm the body, including the cardiovascular system. Smoking, physical inactivity, poor diet and non-compliance with medical treatment are known to bring on or worsen many ailments, ranging from heart disease to the common cold. But there's also evidence suggesting that the mental state of depression itself, independent of any physically unhealthy behaviors, triggers a cascade of hormonal and other changes in the body that damage the heart or blood vessels. Sorting out all these variables and understanding how they interact is a huge theme in medical research.

The inactivity factor

Mary Whooley, MD, an internist and epidemiologist at the San Francisco VA, believes behavior is key. Her team of investigators on the "Heart and Soul Study" followed more than 1,000 heart patients for an average of nearly five years. The goal was to tease out which physiological or behavioral factors were most influential in the pathway from depression to heart disease. Their main finding, reported last fall in the *Journal of the American Medical Association,* was that "the association between depressive symptoms and adverse cardiovascular events was largely explained by behavioral factors, particularly physical inactivity."

Whooley: "Very often, patients with depression don't exercise, which makes them feel more depressed, which in turn leads to their exercising even less. It's a vicious cycle that leads directly to heart disease."

Finkel, who conducts animal and clinical research at VA and West Virginia University, has a different view. He points to experiments in which rats bred to be more

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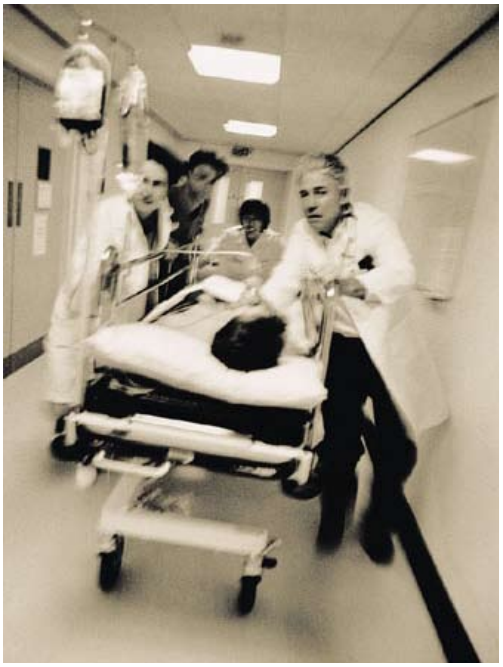
Brokenhearted—Many studies have shown that depression can lead to heart disease. But researchers are still working to unravel how exactly the two diseases are connected.



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susceptible to emotional stress—he says it's a close-enough model for depression—are more likely to go into heart failure when they are restrained.

"Here's an animal model that doesn't have any behavioral issues but is basically programmed differently," says Finkel. He doesn't deny that depression-related lifestyle factors such as smoking or physical inactivity obviously contribute to a higher risk for heart disease. But he asserts that physiological factors that are part of the depression profile—though not necessarily linked to any particular behavior—are just as critical in the equation.

Cardiac abnormalities part of depression

Researchers have identified several biological changes that occur in people with depression, any of which could reasonably make them more susceptible to heart attacks, stroke, heart failure or other cardiovascular maladies: Their hearts beat faster. They tend to have high blood pressure. Their hearts don't adjust well when they switch activities—from walking to sitting, for example. They have sticky platelets, which increases the risk of harmful blood clots. They have low levels of omega-3 fatty acids and high levels of the stress hormone cortisol.

Some of these factors may be aggravated by smoking, say, or poor diet. But Finkel and others believe there are still baseline abnormalities in depressed patients, independent of their unhealthy behaviors. He points out that prenatally stressed rats—his depression model—have some of the same biomarkers.

Heart cells under the microscope—Dr. Mitchell Finkel of VA and West Virginia University and colleague Dr. Fangping Chen examine heart muscle cells from a rat. The team has identified an enzyme that they believe can be "turned off" to help reverse heart failure.

Figuring out how all the lifestyle and biological factors interact is enough to make a researcher's head spin. So why bother? Isn't it enough to simply treat the depression and thereby lower the risk of heart disease, without understanding the exact pathway between the two ailments?

That would make sense, except that treating depression doesn't always appear to improve cardiac health. "There's no strong evidence that treating depression will reduce the risk for heart attack," says Scherrer. This is puzzling to researchers because it seems to mock the well-established notion that depression leads to heart disease. And it makes them even more determined to untangle the factors connecting the two conditions.

Finkel cites a large, federally funded trial that found that while cognitive behavioral therapy modestly improved depression symptoms in heart patients, it did little to cut their risk of further cardiac incidents. Treatment with the antidepressant drugs known as SSRIs, however, reduced the risk of a second heart attack or death by 42 percent.

SSRIs are known to make the blood less likely to clot, and that could be part of why they appear to exert some cardiovascular benefit. "These drugs, independent of the whole mood effect, seem to counterbalance the tendency toward clotting," explains Finkel.

However, there are also studies in which even SSRIs failed to cut the heart risk for depressed patients. In fact, in some trials the drugs actually made things worse from a cardiac standpoint. Regarding these studies,

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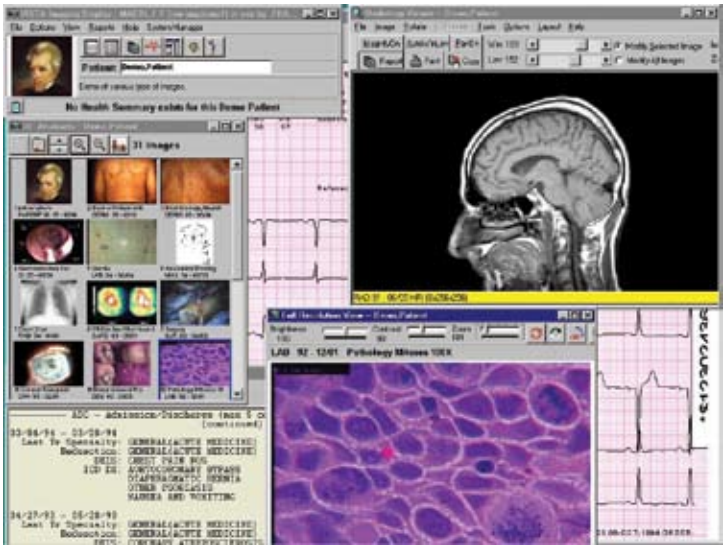
Most U.S. hospitals lack electronic medical records—A team with VA, Harvard and other institutions surveyed nearly 3,000 non-federal hospitals in the U.S. and learned that only 1.5 percent of the facilities have a comprehensive electronic records system available across all major clinical departments. Hospitals were more likely to report having an electronic records system if they were larger institutions, major teaching hospitals, part of a larger hospital system, or located in urban areas. VA is recognized as a pioneer in this area, having implemented its electronic health records system in the late 1990s. (*New England Journal of Medicine,* online March 25, 2009)

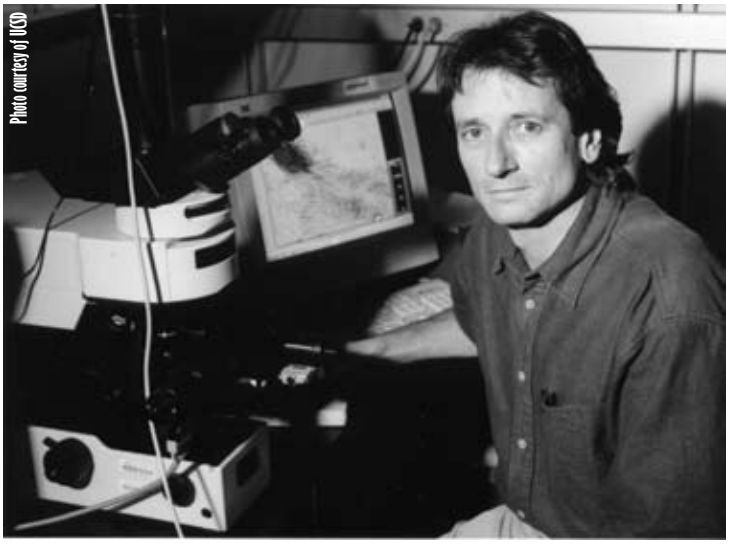
Protein reverses Alzheimer's in animal models—Memory loss, brain cell degeneration and cell death were prevented or reversed in animal models of Alzheimer's disease after treatment with a naturally occurring protein called brain-derived neurotrophic factor (BDNF). A team led by Mark Tuszynski, MD, PhD, of VA and the University of California, San Diego, injected the BDNF gene or protein in a series of cell cultures and animal models. The animals included genetically engineered mouse models of Alzheimer's disease and rats and monkeys that were aged or that had induced damage to a part of the brain that supports memory. In each case, when compared with untreated controls, the animals treated with BDNF performed better on learning and memory tests. And their brains showed restored BDNF gene expression, enhanced cell size, improved cell signaling, and activation in neurons that would otherwise have degenerated. The researchers say the results provide "a rationale for exploring clinical translation to humans." (*Nature Medicine,* Feb. 8, 2009)

Drug risk for seniors—VA researchers and colleagues studied the effects on older adults of multiple prescriptions that act on the central nervous system. *See story below.*



Ahead of the curve—Electronic medical records like those used in VA—illustrated here by a mock screenshot—are in use at only a small percentage of U.S. hospitals, according to a study by authors from VA, Harvard and other institutions. *See story above.*

Elderly at risk from cumulative effects of nervous-system drugs—Many older people have multiple prescriptions for drugs that act on the central nervous system, such as painkillers, tranquilizers or antidepressants. But little research has looked at the negative effects from the combined use of these drugs. Two recent studies by investigators with VA, the University of Pittsburgh and other institutions were among the first to examine the impacts on healthy, community-dwelling seniors of multiple or high doses of these drugs. One study found that higher total daily doses of the medications were associated with recurrent falls. The other found that combined use of the drugs, especially at higher doses, may be linked with cognitive decline. The researchers suggest clinicians should use the lowest possible combined doses of these medications, particularly when treating pain and psychiatric illness that occur together. The studies were part of a larger research project called the Health, Aging and Body Composition Study. (*Journals of Gerontology Series A: Biological Sciences and Medical Sciences,* online Feb. 4, 2009; *Journal of the American Geriatrics Society,* February 2009)



Seeking Alzheimer's cure—A team led by Dr. Mark Tuszynski, of VA and the University of California, San Diego, was able to reverse memory loss in primates by injecting a naturally occuring brain protein. *See story on facing page.*

Compound in saffron shows promise for pancreatic cancer—A team at the Cancer Research Unit at the Kansas City (Mo.) VA, led by Sushanta Banerjee, PhD, conducted a series of experiments to verify the anti-tumor properties of crocetin—a compound derived from the spice saffron that has long been used in traditional medicine against cancer and other diseases. The researchers found that crocetin was effective in thwarting tumor growth both in cell cultures and in mice that had been injected with pancreatic cancer cells. (*Molecular Cancer Therapeutics,* February 2009)

Grape-derived antioxidant stops lung tumors in lab study—Lab experiments at the Birmingham (Ala.) VA showed for the first time that proanthocyanidins—an antioxidant compound found in grape seeds, pine bark and other natural sources—could halt the spread of lung cancer in cell cultures and mice. The research, led by Santosh Katiyar, PhD, used mice that had been implanted with human non-small cell lung cancer, the most common form of the disease. According to the authors, their preclinical findings suggest that proanthocyanidins, which are taken as a dietary supplement by many consumers worldwide, hold promise for lung-cancer prevention and treatment. (*Clinical Cancer Research,* Feb. 1, 2009)

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Whooley notes: "The tough part is to sort out whether it's just because the people on antidepressants have worse depression. It may be that the worse the depression, the worse the cardiovascular disease. And antidepressant use may just be a marker of worse depression, rather than a mechanism between the depression and the cardiac event."

Whooley's "Heart and Soul Study" suggests a different, less invasive angle of intervention: Get people to exercise—a proven remedy for depression and the heart. Says Scherrer, "Exercise is an excellent prescription for all patients, including those with depression."

Integrating physical and mental health care

Even though the mechanistic link between depression and cardiovascular disease is still murky, and studies have thus far not conclusively shown that treating depression helps the heart, Scherrer and others say depression should be formally recognized as a major cardiovascular risk factor. He says studies have shown it to be at least as important as diabetes or hypertension in this regard.

The American Heart Association's website acknowledges that "individual response to stress" may play a role in heart disease but stops short of listing depression as a full-fledged modifiable risk factor.

Nonetheless, many cardiologists are realizing they need to be more aware of depression's role in heart disease. And conversely, according to Scherrer, psychiatrists should do more cardiovascular screening. "Psychiatrists are fully trained medical doctors," he says, "but how often do they pull out the stethoscope? Do they ever check blood pressure? Why can't some basic screening be incorporated into the treatment of psychiatric patients?"

VA may be ahead of most health systems in integrating mental and physical care, notes Scherrer.

Patricia Dubbert, PhD, a psychologist and researcher at the G.V. (Sonny) Montgomery VA Medical Center in Jackson, Miss., agrees. "In our hospital, we try really hard with our mental health patients to make sure they're in primary care, which would do that type of screening," says Dubbert. "But it is more difficult to get some mental health patients into primary care, so that's where I agree with the idea of bringing that type of screening into mental health care. Wherever the patient will go, that's where we need to provide the care." Ideally, she says, care should "be integrated in a way that primary care providers have ready access to mental health

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expertise and patients with mental illness have ready access to primary care."

Part of the answer may lie in collaborative care—an increasingly popular model in VA.

The agency recently funded John Rumsfeld, MD, PhD, of the Denver VA Medical Center, to test a new model of heart-failure care that emphasizes multidisciplinary teams including a primary care doctor, cardiologist and psychiatrist. Managing depression will be integral to the project.

Whether treating depression among the VA patients in the study will ease their heart burden—and reduce their risk of dying—remains to be seen. But even cardiologists are quick to point out that helping patients cope with depression is itself critically important.

Finkel: "We as cardiologists tend to be very focused on whether the depression treatment is going to improve survival. But depression is a horrible disease. You really see this when you take care of depressed patients. It almost makes you cry."

INVESTIGATOR SNAPSHOT

Memorable prosthetics lesson—Brian Ruhe, MS, lost both legs in a car crash at age 18. Today, 16 years later, he is a promising biomedical engineer working toward his doctorate at VA's Chicago Motion Analysis Research Laboratory and Northwestern University. Ruhe also reaches out to others—including Veterans and students—to share his experiences and knowledge. He is seen here talking with eighth-graders at Chicago's Frances Xavier Warde School about the biomechanics of walking with prostheses.

Ruhe's research is funded by the National Institute on Disability and Rehabilitation Research. He studies balance in people who have had one leg amputated above the knee. Current models of prosthetic feet do not adjust well to slopes. This can cause balance difficulties and lead to muscle strain and fatigue for users. Ruhe hopes the data he is collecting will help in the development of algorithms to control advanced ankle mechanisms that will allow for improved balance.