



Exploring insulin's role in Alzheimer's disease

A recent pilot study by VA researchers found that a nasal insulin treatment improved memory, thinking skills, and functional ability in people with Alzheimer's disease or its precursor, mild cognitive impairment. Currently, there are no effective treatments to delay or prevent Alzheimer's.

Suzanne Craft, PhD, and colleagues with the Geriatric Research, Education and Clinical Center at the VA Puget Sound Health Care System led the trial, which was sponsored by the National Institute on Aging. The findings appeared in the Sept. 12 *Archives of Neurology*.

The study built on previous research—by Craft's group and others—that linked

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Can Vitamin D slow prostate cancer?

Like other African American men, Cassie Watson, of Goose Creek, S.C., knew he was at higher risk for prostate cancer than U.S. men in general.

Now, at age 65, Watson has the disease. Fortunately, his tumor appears to be slow-growing, and he and his doctor have chosen to manage it through “active surveillance,” formerly known as “watchful waiting.”

That means Watson gets tested more frequently—prostate-specific antigen (PSA) tests, digital rectal exams, and biopsies—to make sure the cancer isn't spreading.

But that's not all he's doing. Watson is also taking part in a study at the Charleston VA Medical Center to see if

vitamin D has any effect in keeping the cancer in check. The new trial will include up to 88 men, about half African Americans, all with early-stage prostate cancer.

Lead researcher Sebastiano Gattone-Celli, MD, says yet-unpublished results from an earlier study with some 45 patients from the Charleston VA were encouraging. The previous trial was “open label,” whereas the new one will be randomized and single-blinded—meaning patients will not know whether they are getting a mock vitamin D supplement or the real thing. That discounts any difference in the “placebo effect” between the two groups.

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Vitamin vigil—Cassie Watson is taking part in a study to see if vitamin D can slow prostate cancer, as an adjunct to the treatment strategy known as active surveillance, or watchful waiting.

INSULIN *(from page 1)*

low brain levels of insulin to Alzheimer’s. Insulin helps turns sugar in the bloodstream into energy for cells. In type 1 diabetes, the pancreas doesn’t make enough insulin, and in type 2 diabetes, which affects nearly one in five VA patients, the body is resistant to the hormone’s effects.

But insulin’s role goes beyond blood-sugar metabolism and diabetes: It plays a key role in brain aging in general, and in several chronic diseases. So its connection to Alzheimer’s is not surprising, says Craft, who is also a professor of psychiatry and behavioral sciences at the University of Washington.

VA Research Currents spoke with Craft to learn more about the intriguing link among diabetes, insulin, and Alzheimer’s disease.

When did researchers first start to see a connection between diabetes and Alzheimer’s disease?

It’s been observed for quite some time, through imaging techniques such as positron emission tomography, that patients with Alzheimer’s have reduced glucose

metabolism in certain areas of their brain. In the early 1990s, there were studies by several groups looking at whether supplementing glucose might overcome that deficiency, at least temporarily.

We conducted a study in which we gave patients with Alzheimer’s a glucose-rich drink to see how it affected their memory. We were able to improve their memory somewhat, but the improvement was associated most closely with the rise in insulin levels that occurred. Generally, whenever glucose is raised, insulin is raised as well, as the body produces insulin to help metabolize glucose. In a later study, in which we were able to raise glucose but block the release of insulin, we found there was no longer any memory improvement. That showed us it was actually insulin, not glucose, that was critical.

A Japanese epidemiologic study came out in *Neurology* on Sept. 20 showing a strong link between diabetes and Alzheimer’s disease. It seems this study complements yours.

I don’t think it’s entirely a coincidence, although there’s no link between the two studies other than the topic they both deal with. When you look at how scientific knowledge accumulates, some describe it as a wave—you have this slow build-up, and then the studies begin to converge and “feed” on one another, if you will, and you get this crashing wave. I’d like to think we’re at that point where we’re going to get a lot of acceleration in this area.

Over the past five years, the converging evidence has come not just from epidemiologic studies and our clinical work, but from the basic science work as well, showing a very close relationship between insulin and beta amyloid, the protein that collects in the brain of patients with Alzheimer’s disease. The two substances regulate each other in the brain. Another set of data both from animal studies and our

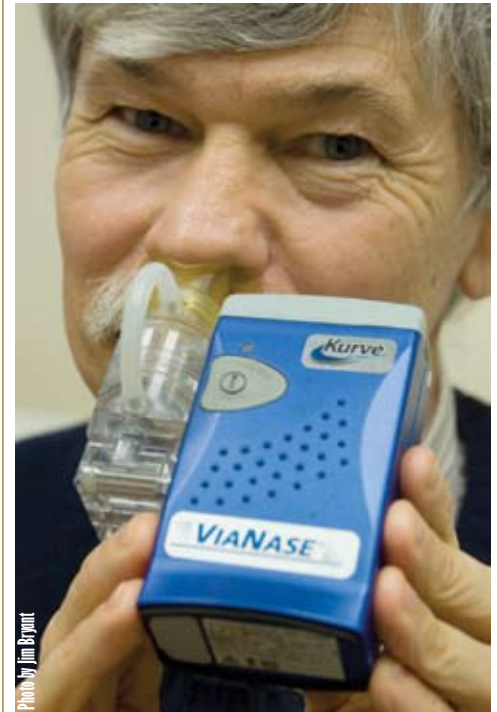


Photo by Jim Bryant

Special delivery—Dr. Bill Banks of the VA Puget Sound Healthcare System demonstrates a nasal applicator used to deliver insulin—or potentially other therapeutic substances—quickly and directly to the brain. In the photo on page 1, he is seen with lead researcher Dr. Suzanne Craft.

human studies show that insulin plays an important role in synaptic health. The formation of links between synapses—the structures that allow for the passage of signals from one brain cell to another—is thought to be the physiological underpinning of memory. So the evidence is coming now from a number of different directions, and that’s what we need to begin to address a very complex, multifactorial disease like Alzheimer’s.

Once you identified the effects of insulin on the brain, what was the next phase of your research?

We gave insulin intravenously. We were able to do this without lowering blood sugar by co-administering a small dose of dextrose. We found that this procedure

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103 S. Gay Street, Rm. 517
Baltimore, MD 21202
(410) 962-1800, ext. 223
research.publications@va.gov

Editor: Mitch Mirkin

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Research on schizophrenia genes spans oceans

It's a long way from the rugged green hills and palm-lined beaches of Puerto Rico's northern coast to the Bronx VA Medical Center and Mount Sinai Medical Center in New York City.

But the distance is no barrier to scientists seeking to solve the genetic puzzle of schizophrenia, a potentially devastating mental illness that affects some 100,000 VA patients and more than two million Americans.

A Bronx team, with help from the San Juan VA, has been studying genetic risk factors for schizophrenia among countryside-dwelling Puerto Ricans and their New York-based relatives. The project is one of several in which the Bronx scientists and other VA investigators are seeking genetic clues that could translate to better therapies for Veterans and others with serious mental illness.

The research ranges from efforts such as the Puerto Rican study—focused initially on one large extended family—to studies that include diverse, nationwide samples of Veterans, and others with international partners and tens of thousands of patients around the globe.

The Puerto Rican genetics project has an interesting background. Lead investigator Jeremy Silverman, PhD, traces it

back to work that began in 1989, funded by the National Institute of Mental Health.

“We were funded to study families in this area with multiple members with schizophrenia,” recalls Silverman. “There were 12 families in all, and one was a large nuclear family, originally from Puerto Rico.” Looking at all the genetic results combined, the researchers found a strong region of interest on the short arm of chromosome 5. The chromosome, among 23 pairs of chromosomes found in each cell in the body, is thought to have more than 1,000 genes in all, among the 25,000 or so genes in the human genome. The Bronx team's probes highlighted an area on the chromosome containing about a dozen genes, one or more of which could be key in determining the traits that define the disease.

Further study revealed it was actually the DNA from the one large family that was generating the “strong positive signal.” Silverman's group began working with the San Juan VA to locate additional members of the clan, who lived mainly in two rural Puerto Rican towns: Vega Alta and Corozal, both about 30 minutes west of San Juan.

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Worldwide gene hunt—Based at the Bronx VA Medical Center in New York City, Dr. Jeremy Silverman, seen here in center photo with molecular geneticist Dr. Irina Beshpalova and research coordinator Rui Ferreira, studies the genetics of schizophrenia, particularly among Puerto Ricans. His team also contributes to international research that includes populations in Scandinavia, Europe, and many other regions.

'ACT' psychotherapy effective for pain

A study at the VA San Diego Healthcare System found that a relatively new form of psychotherapy known as Acceptance and Commitment Therapy, or ACT, was as effective as standard cognitive behavioral therapy for helping patients cope with chronic pain. The trial included 114 people who had been experiencing chronic pain for an average of 15 years, due to causes such as arthritis, neuropathy, or degenerative disc disease. They were randomized to eight weeks of either cognitive behavioral therapy or ACT, which teaches mindfulness techniques and helps patients work on accepting their condition. According to lead author Julie Wetherell, PhD, "We found that both treatments reduced pain interference, anxiety, and depression, but patients who received ACT reported higher levels of satisfaction with treatment." She adds that ACT is already being taught to therapists throughout VA as an effective depression treatment. (*Pain*, September 2011)

'Cav-1' protein spurs brain-cell growth

An anesthesiology research team with VA and the University of California, San Diego, showed that targeting brain cells with a protein called caveolin-1 (Cav-1) causes them to sprout new dendrites, the tree-like projections that receive electrical signals from other neurons. Administering Cav-1 also boosted other markers of neuron growth and regeneration. The researchers had previously shown that the loss of Cav-1 in the brain resulted in neurodegeneration and aging in young mice. The research group, part of the Cardio/Neuro Protection Laboratories at the San Diego VA and UCSD, is now using gene therapy to target caveolin-1 to neurons in animal models of traumatic brain injury and other neurodegenerative disorders. According to lead researcher Brian Head, PhD, a VA Career Development awardee, "The use of this novel approach may serve to reverse or limit neurocognitive decline and neurodegeneration associated with aging, trauma, Alzheimer's, Parkinson's, spinal cord injury, and various other neurologic diseases." (*Journal of Biological Chemistry*, Sept. 23, 2011)

Gulf War follow-up tracks health changes

VA researchers looked at changes in health between 1995 to 2005 among Veterans who had been deployed to the Persian Gulf for operations Desert Storm and Desert Shield, and those who had served during the same era but had not been deployed to the Gulf. The 2005 follow-up study included 5,469 deployed and 3,353 non-deployed Veterans who had also taken part in the 1995 baseline study. The 2005 data, based on mailed surveys and phone interviews, showed that deployed Veterans were more likely to report poor health in terms of limitations on daily activities, repeat clinic visits and hospitalizations, chronic fatigue symptoms, posttraumatic stress disorder, and self-perceived health status. According to the study authors, during the 10-year period, "The health of deployed Veterans worsened in comparison with nondeployed Veterans because of a higher rate of new onset of various health outcomes and greater persistence of previously reported adverse health on the indices." For complete information on VA's Gulf War research and care, visit www.publichealth.va.gov/exposures/gulfwar/index.asp. (*American Journal of Epidemiology*, October 2011)



Gulf gear—Wearing gas masks and protective gear, soldiers from the 82nd Airborne Division acclimate to the Saudi heat during Operation Desert Shield in 1990.

IoM burn pit report

The Institute of Medicine released a VA-commissioned report titled "Long-Term Health Consequences of Exposure to Burn Pits in Iraq and Afghanistan" on Oct. 31. For a link to the report and more information on this topic, visit www.publichealth.va.gov/exposures/burnpits.

SCHIZOPHRENIA (from page 3)

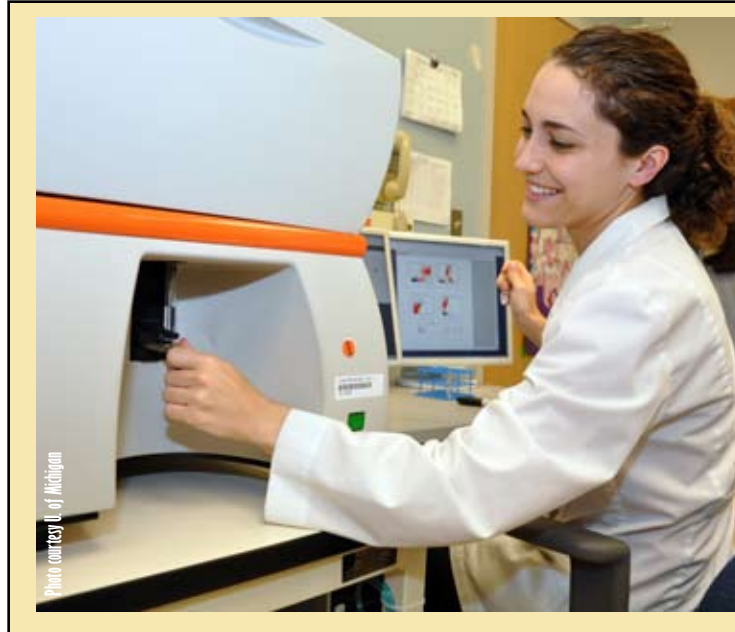
By comparing family members with schizophrenia to those free of the disease, the researchers could zero in on target genes that boost the risk of disease. The research has been ongoing for two decades, expanding to include other Puerto Ricans beyond the original family.

A study published in late 2010 by Silverman's group homed in on a gene known as AMACR. It codes for an enzyme that helps metabolize fatty acids. Mutations in the gene may play a key role in schizophrenia risk, the researchers believe, especially in men.

Silverman says Puerto Ricans as an ethnic group are under-studied from a genetics standpoint. As a result, important knowledge might be forfeited, because "there is increased homogeneity within this population, compared with studying the U.S. mainland, or even Europeans, or African Americans, or Hispanics as a whole." Silverman explains that studying a group that is similar genetically narrows the number of genes potentially involved in a disease and makes the search somewhat less complex. Many schizophrenia genetics studies have been conducted, for example, among relatively homogenous peoples such as Icelanders and Swedes.

An alternative approach that genomics researchers use is studying huge, diverse populations. "You can get tens of thousands of patients and still get signals even in a very heterogeneous population because of the large size of the sample," says Silverman.

That was the case in a study published in *Nature Genetics* in September 2011. Researchers discovered new "regions of interest" that could eventually link specific genes to schizophrenia and what appears to be a genetically related mental illness,



Honored—Dr. Christine Freeman was one of four recent VA winners of the Presidential Early Career Award for Scientists and Engineers. She studies chronic obstructive pulmonary disease at the VA Ann Arbor Healthcare System. Learn more at www.research.va.gov/currents.

bipolar disorder. The genome-wide association study involved some 250 scientists in more than 20 countries. Silverman and three other VA investigators were part of the effort.

So far, studies of different types and in different settings have yielded a mixed bag of genetic clues, pointing to different regions on different chromosomes. But that's not surprising, given the complexity of the disease, says Silverman.

"Schizophrenia is a disease that can look different clinically, biologically, genetically. There's tremendous heterogeneity. So it makes sense that there are different genes that are going to contribute to risk in different populations." He hopes his group's research will make an important contribution at least with regard to schizophrenia among Puerto Ricans, if not more widely.

One factor that helps in the quest is the VA electronic health record system. Health information found in the records—such as other conditions patients have, how they respond to certain medications, or what environmental exposures they may have had—can help make sense of genetic data.

Schizophrenia research in VA also allows researchers to tap into a group that, despite its ethnic and racial diversity, is in one sense genetically homogenous. That's because Veterans with schizophrenia generally developed the disease relatively late in life, after their joining the military. Usually, the disease emerges by the late teens. This late-onset Veteran population, like the extended Puerto Rican family studied by Silverman's group, is likely to have a smaller set of disease-linked genes than the schizophrenia population at large.

Still, there's a long road ahead. Silverman acknowledges that scientists need to learn far more about the genetic underpinnings of schizophrenia before there's a firm basis for new drug development. "We get excited when we get strong evidence tying certain genes to schizophrenia," he says, "but the extent to which these genes may account for overall disease risk may still be relatively weak. We're still far from identifying some cause that we can really start to build interventions around." He is confident, though, that the cumulative work of scientists around the globe will eventually enable a breakthrough. —

Clinical trial: Copper in hospital rooms kills germs

A study conducted at the Charleston (S.C.) VA Medical Center, Medical University of South Carolina, and Sloan Kettering Cancer Center in New York found that the use of antimicrobial copper surfaces in intensive care unit rooms cut the amount of bacteria by 97 percent and resulted in a 41-percent drop in the rate of hospital-acquired infections.

Results from the clinical trial were presented Oct. 21 at the annual meeting of the Infectious Diseases Society of America. The \$7.7 million study was funded by the Army's Telemedicine and Advanced Technologies Research Center, following an initial lobbying effort by the Copper Development Association, part of the International Copper Association, a trade group.

Copper, known since ancient times for its antimicrobial properties, is recognized by the U.S. Environmental Protection Agency, based on EPA lab tests, as the only touch surface to continuously kill certain bacteria—including common drug-resistant *Staphylococcus aureus* (MRSA). Such germs pose a major public health threat and result in some 100,000 deaths and \$45 billion in health costs each year in the U.S., according to the Centers for Disease Control and Prevention.

At the Charleston VA, surfaces such as bed rails, tray tables, nurse call buttons, and IV poles were replaced with antimicrobial copper versions as part of the study. Preliminary research had determined which surfaces in patient rooms were most likely to carry harmful germs.

The Charleston arm of the study was led by infectious-disease specialist Joseph John, MD, who called copper an “amazing material.” He said the fact that copper is



The copper effect—Copper components such as bed rails and an over-bed tray were installed in this ICU room as part of a three-site study on the metal's germ-killing effects.

always active in killing bacteria, without any human intervention, “makes it an ideal second line of defense to good infection control practices.”

Copper's chemical effect on germs may be something akin to electrocution.

His study counterpart at Sloan Kettering, Kent Sepkowitz, MD, told *Crain's Health Pulse*, “We were stunned by the results.” He added that while scientists don't know exactly how copper kills microbes, the chemical effect may be something akin to electrocution.

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INSULIN (from page 2)

improved memory. But this was only a proof of concept: If you administer insulin systemically, you have to be very careful to keep people's blood sugar stable, because the insulin could make it drop too low. Also, having very high levels of insulin chronically in the periphery is not good, the same way having high levels of glucose is not good. So you really need a way to get insulin into the brain.

That's where the nasal applicator comes in. How does it work?

It's an investigational device that is similar to a nebulizer, in that it has a droplet generator. It takes the liquid drug and projects it in a vortex that reaches the uppermost part of the sinuses. With a typical nose spray, most of it ends up in the bottom of your throat.

To read more of this interview, go to www.research.va.gov/currents.

PROSTATE *(from page 1)*

Vitamins have been knocked in the press lately, especially with regard to prostate cancer. A major government-funded study, known as SELECT, found that vitamin E didn't help prevent the disease—in fact, if the study results are valid, the vitamin could even raise the risk.

There's some debate among experts over what to make of the findings from SELECT. At any rate, the new VA study in Charleston, aside from testing a different vitamin, will also be distinct in this regard: All the study volunteers are low in the vitamin to begin with. Vitamin D deficiency is widespread in the U.S. and has been linked to any number of health conditions, from brittle bones to tiredness, low mood, and mental fog.

African Americans at higher risk for low vitamin D

The trial is especially relevant for African Americans: Besides their higher prevalence of prostate cancer, they are also at greater risk for vitamin D deficiency. Genetically, the melanin in their skin was designed to screen out some of the intense sunlight found in Africa. Living a typical Western lifestyle in North America, though, African Americans tend to not absorb adequate sunlight. Vitamin D is generally not found in food, so aside from taking supplements, the only effective way to boost levels is through sun exposure. That strategy hikes the risk of skin cancer, though, so doctors generally advise people who need more vitamin D to take supplements.

At the very least, the Veterans in the new study who receive the vitamin—versus a placebo—are likely to see some overall health benefits as their vitamin D levels



Possible prostate protector—Vietnam Veteran Cassie Watson, seen here with his physician, Dr. Stephen Savage (right), and lead researcher Dr. Sebastiano Gattoni-Celli, is taking part in a clinical trial at the Charleston VA to determine if vitamin D can slow the progression of prostate cancer.

reach recommended levels. According to Gattoni-Celli, vitamin D affects some 800 genes and a “huge number of organ systems.” In fact, because vitamin D is thought to help in conditions such as high blood pressure and diabetes, which are more common in minorities, Gattoni-Celli asserts, “If you replete African Americans with vitamin D, I think a lot of health disparities would disappear.”

Whether the nutrient can slow prostate cancer remains to be proved. In a recent review in the journal *Advances in Preventive Medicine*, a team with the Mayo Clinic acknowledged strong preliminary findings but concluded that “whether [vitamin D] it can effectively prevent the development and/or progression of prostate cancer in humans remains ... inconclusive and an intensively studied subject.”

Gattoni-Celli asserts that “the evidence linking vitamin D to prostate cancer [in lab and epidemiologic studies] is extremely

robust.” He says he is confident the vitamin can not only slow the disease, but prevent it as well.

‘I think about it, but I don’t worry about it’

Cassie Watson and the other Veterans in the new study will take either 4000 international units (IUs) of vitamin D each day for a year, or a placebo, packaged to look identical to the vitamin. Biopsies will be taken at the study’s end, as part of the Veterans’ standard medical care, to gauge the growth of the tumors. Results are expected in late 2013.

Meanwhile, Watson, who served in Vietnam with an Air Force security unit, says he tries to go about his life and not worry about the cancer within him. “I think about it, but I don’t worry about it. I know how to pray.” —

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Gene variant found to double rate of mental decline

A variation in the coding pattern of a single gene significantly affects the rate at which men's intellectual function drops as they grow older, suggests a study by a team with the VA Palo Alto Healthcare System and Stanford University.

In a study published online Oct. 25 in *Translational Psychiatry*, researchers tested 144 middle-aged and older airplane pilots on flight simulators, three times over two years, and found that having one version of the gene versus the other version doubled the rate of declines in performance.

The genetic variation implicated in the study has been linked previously to several psychiatric disorders. The VA-Stanford study provides the first evidence of its impact on skilled task performance in the healthy aging brain, says senior author Ahmad Salehi, MD, PhD.

Using MRI brain scans, the researchers also found greater volume loss in the hippocampus—a brain region crucial to memory and spatial reasoning—in pilots with the genetic variant.

The gene in question codes for brain-derived neurotrophic factor, or BDNF, a key protein in the central nervous system.



Pilot study—Dr. Joy Taylor oversees a flight simulation test at a VA-Stanford University lab. She and her colleagues recently reported on a genetic variant found to affect mental decline.

Usually, the BDNF gene dictates that the amino acid valine be present in a particular spot on the protein. A less common variant results in a different amino acid, methionine, residing in that same location. The variant has been linked to higher risk for depression, stroke, anorexia nervosa, anxiety-related disorders, suicidal behavior, and schizophrenia.

Based on DNA samples, 55 of the 144 men in the study were found to have at least one copy of a BDNF gene with the methionine variant. Performance dropped more sharply among these pilots over the two-year study, even after researchers adjusted for the pilots' level of experience and other factors that could affect performance. A longer follow-up study is in now in the works.