Fatty liver disease: a new epidemic?

Hardly a day passes without media reports of America’s skyrocketing rates of obesity and type 2 diabetes. Far fewer people, though, are familiar with another disease—closely linked to the first two—that experts say is also becoming an epidemic.

Nonalcoholic fatty liver disease—excess fat in the liver—affects as many as one in five Americans, according to the American Liver Association. But for those with diabetes, says VA physician-researcher Kenneth Cusi, MD, the rate may be as high as four in five. Given that more than a quarter of VA patients are diabetic, fatty liver disease is likely to move up quickly on VA’s agenda of targeted health issues over the next few years.

The disease itself has no symptoms, even when it advances to a more serious form called non-alcoholic steatohepatitis (NASH).

New genomics lab in Little Rock will move VA toward ‘personalized medicine’

When patients receive the anti-clotting drug warfarin, commercially known as Coumadin, the dose has to be just right: Too little won’t prevent clots, and too much can cause severe bleeding.

Until recently, doctors would have to carefully monitor patients over several visits to fine-tune their dose. Now, with a small sample of a patient’s DNA—usually from a cheek swab or blood draw—doctors can run a genetic test and predict the proper dose from the outset.

“Patients still need to be monitored, but at least we can get close from the start,” says Steven Schichman, MD, PhD, chief of hematopathology and molecular diagnostics at the Little Rock VA Medical Center. The warfarin test is an example of the work Schichman will be overseeing as head of VA’s first Pharmacogenomics Analysis Laboratory (PAL), funded with $825,000 from VA’s Office of Research and Development.

The new lab—an outgrowth of a molecular diagnostics lab Schichman has run since the 1990s—will also do tests for veterans who need irinotecan, or Camptosar, a colon-cancer drug. Certain patients need more of the drug, but too high a dose can block breathing and cause other serious side effects. “We’ll be testing for a certain enzyme involved in the metabolism of this drug,” explains Schichman. “If we can predict which patients are fast or slow metabolizers, we can adjust the dose and get it right the first time, so the drug is at its full therapeutic level but doesn’t...
have the toxicity of an overdose.”

Testing on behalf of individual VA patients—for warfarin, irinotecan and eventually many other drugs—is only part of what the PAL will do. But this in itself is an important step toward “personalized medicine,” says Schichman. “We’re looking at people’s genetic makeup and using that information to tailor therapy, to select the drug that’s best for them, and to select at least a starting dose that’s most appropriate.”

The PAL will also be a research lab for VA’s Cooperative Studies Program, which runs clinical trials involving up to thousands of patients at multiple sites. Researchers will collect DNA samples from study volunteers—along with their clinical information—and the PAL will scan the genetic material to see if certain variations are associated with particular medical conditions.

Today’s methods allow for fast, efficient DNA scanning

The scanning is done through a super-efficient method called “high throughput genotyping.” The process relies on commercially available chips encoded with up to half a million or so common genetic variations. Scientists now have a complete picture of humans’ genetic structure, thanks to the much-publicized Human Genome Project and other gene-mapping efforts.

‘We’re looking at people’s genetic makeup and using that information to tailor therapy.’

By scanning huge batches of DNA for the variations encoded on the chips, researchers have already linked some of these variations—known as single-nucleotide polymorphisms, or SNPs for short—to diabetes, breast cancer and other diseases. The concept has been around a while, but the mind-blowing speed and relative ease of the new technology allows for the statistical power researchers need to show meaningful links between genetic variations and diseases.

Linking genetic variations to disease is only part of the puzzle

Schichman acknowledges that linking a SNP to a particular health condition is one thing, but understanding how exactly the risk plays out is quite another. Genetic variations may determine our health to a large extent, but only through an amazingly complex process that involves multiple genes and any number of environmental factors.

“One once the associations are pinpointed, the science needs to be done to show mechanistically how those associations may lead to, for example, higher susceptibility to a certain cancer,” says Schichman. His lab team will work with molecular epidemiologists at the Little Rock VA and other sites to plan research and analyze the data that’s collected.

Even though there’s much work yet to be done, Schichman compares the completion of the human genome and the new technology it has spawned to a burst of light that is enabling exponential progress. “It’s really very exciting. I started in this field a long time ago, and we were in the dark about so many things. Now, there’s so much more that we can do.”
Muscle-repair research yields insights on adult stem cells

A discovery by a VA-Stanford group studying muscle-tissue regeneration may help settle a decades-old debate about the ability of adult stem cells to prevent cancer in the body.

The findings are from the lab of Thomas Rando, MD, PhD, chief of neurology and director of the Geriatric Research, Education and Clinical Center at the Palo Alto VA, and associate professor of medicine at Stanford University School of Medicine and deputy director of the school’s Center on Longevity. His group studies the potential role of adult stem cells—which help regenerate tissue in the body—in therapies for neurodegenerative disease, traumatic injury, diabetes and other conditions.

The new study results suggest that when adult stem cells undergo cell division, random mutations in their chromosomes are not passed on to the next generation of stem cells. This could explain why cancer isn’t more common than it is, and offer support for a controversial hypothesis proposed more than 30 years ago by Oxford University geneticist John Cairns, PhD. Although other groups have uncovered hints that Cairns was right, Rando’s findings, published in May in the Public Library of Science-Biology, are the most detailed to date.

Stem cells exhibit cancer-avoiding behavior

Stem cells in adult tissues such as muscles or bone marrow survive the lifetime of an animal, dividing when needed to replace cells lost to wear and tear. Every time one of the cells divides, it produces one offspring that becomes a new stem cell and one shorter-lived cell that replaces body tissue. During replication, the original cell “photocopies” its genome and gives one set of chromosomes to each of the two new cells. Each round of photocopying introduces genetic errors, or mutations, some of which could derail essential functions and lead to cancer.

Researchers have wondered why stem cells don’t morph into cancer more often, given all the accumulating mutations. Cairns’ “immortal strand hypothesis” was that adult stem cells might avoid cancer by shuffling off the “photocopied”—and error-ridden—chromosomes to those new cells designated as tissue cells, and keeping the error-free originals for those destined to remain stem cells. Cairns reasoned that mutations, which could take years to develop into cancer, would be of far less consequence in short-lived body cells than in long-lived stem cells.

Other scientists have asserted that original and replicated chromosomes are distributed randomly between new stem cells and body-tissue cells, with no such natural scheme to avert cancer.

The new evidence in support of Cairns emerged after Michael Conboy, PhD, a postdoctoral fellow in Rando’s lab, repeatedly found the same troubling artifact in an experiment. The group had been studying how muscle stem cells divide in the days following an injury. Their DNA-labeling system, by way of analogy, inserted different color “paper” in the cell’s “photocopier” each day. Based on the color of the photocopied chromosomes, they’d know what day the cell divided.

Conboy had expected that after each round of division, both offspring cells would inherit some original, uncolored chromosomes and some colored ones. However, even after months of painstakingly repeated experiments, the offspring stem cell’s chromosomes remained stubbornly uncolored. In similar experiments with normal muscle cells rather than stem cells, those cells behaved exactly as expected, incorporating the colored chromosomes into both newly formed cells.

New evidence supports decades-old theory

“We kept thinking, this must be wrong—maybe we added the labels wrong,” Rando recalls. Eventually the group realized that the only logical explanation was that the offspring stem cells eschewed any copied chromosomes in favor of the error-free originals, exactly as Cairns proposed. Once they accepted this explanation, they devised experiments to specifically look for proof of Cairn’s hypothesis. Those results are what appear in PLoS-Biology.

The work was supported by the National Institutes of Health through an NIH Director’s Pioneer Award to Rando.

Adapted, with permission, from an article in the April 18 Stanford Report.
Recent publications and presentations by VA investigators

Below is a brief sampling of recent publications and presentations by VA investigators, based on notifications received by R&D Communications (see reporting requirements at www.research.va.gov/resources/policies/pub_notice.cfm.) Every attempt is made to present a cross section of investigators, topics and medical centers. Only VA-affiliated authors are listed here, due to space constraints.

“Assessing an Organizational Culture Instrument Based on the Competing Values Framework: Exploratory and Confirmatory Factor Analyses.” Christian D. Helfrich, MPH, PhD; Yu-Fang Li, PhD; David C. Mohr, PhD; Mark Mekerko, PhD; Anne E. PhD, RN. Seattle, Boston. Implementation Science, April 25, 2007.


“Impact of Oral Anti-Hyperglycemic Therapy on All-Cause Mortality Among Patients with Diabetes in the Veterans Health Administration.” Kristijan H. Kahler, PhD; Mangala Rajan, MBA; Monika M. Safford, MD; Leonard M. Pogach, MD. East Orange, Birmingham. Diabetes Care. April 17, 2007.

“Implementation of Buprenorphine in the Veterans Health Administration: Results of the First Three Years.” Adam J. Gordon, MD, MPH; Jodie A. Traifton, PhD; Andrew J. Saxon, MD; Allen L. Gifford, MD; Francine Goodman, PharmD, BCPS; Vincent S. Calabrese, PharmD; Laura McNicholas, MD, PhD; Joseph Liberto, MD. Pittsburgh, Palo Alto, Seattle, Bedford, Hines, Philadelphia, Baltimore, Drug and Alcohol Dependence. May 8, 2007.

“Loss of WISP-2/CCN5 Signaling in Human Pancreatic Cancer: A Potential Mechanism for Epithelial-Mesenchymal-Transition.” Gopal Dhar, PhD; Smitha Mehta, PhD; Snigdha Banerjee, PhD; Sharad C. Mathur, MD; Suman Kambhampati, MD; Sushanta K. Banerjee, PhD. Kansas City. Cancer Letters. March 23, 2007 (online).


“Patient and Provider Perceptions of Hypertension Treatment: Do They Agree?” Peter J. Kaboli, MD, MS; Michael S. Henderson, MA; Mitchell J. Barnett, PharmD, MS; Areej Ishini, MD, MS; Barry L. Carter, PharmD. Iowa City, Minneapolis. Journal of Clinical Hypertension. June 2007.

“Quality-of-Life Outcomes of Treatments for Cutaneous Basal Cell Carcinoma and Squamous Cell Carcinoma.” Mary-Margaret Chren, MD; Anju P. Sahay, PhD; Daniel Bertenthal, MPH; Saunak Sen, PhD; C. Seth Landefeld, MD. San Francisco. Journal of Investigative Dermatology. June 2007.


“Veterans Seeking Treatment for Posttraumatic Stress Disorder: What About Comorbid Chronic Pain?” Jillian C. Shepherd, PhD; Megan Keyes, PhD; Tanja Jovanovic, PhD; David J. Ready, PhD; David Baltzell, MD; Virginia Worley, LICSW; Vanessa Gordon-Brown, MD; Cantrina Hayslett, MA; Erica Duncan, MD. Boston, New Orleans, Atlanta. Journal of Rehabilitation Research and Development. Vol. 44. No. 2, 2007.
Engineers seek smoother, more natural control of prosthetic arms

You want to be able to hold a cup of coffee without crushing it, or have a conversation with someone across the table and look them in the eye while sipping your coffee.

Those may sound like modest goals for an amputee using an artificial arm and hand. But according to Ron Triolo, PhD, longtime investigator at VA’s Functional Electrical Stimulation (FES) Center and executive director of the agency’s more recently established Advanced Platform Technology (APT) Center, such tasks are indeed challenges for upper-limb amputees—even when they have the most advanced prostheses on the market. “It’s difficult because you have to attend to the artificial hand and not the other person in the room,” he says. “You can’t concentrate on anything else while you’re paying attention to your terminal device.”

Two VA centers collaborate on Army-funded project

Changing that reality is the goal of a team of engineers at the Cleveland-based FES and APT centers. The centers, both joint efforts between VA and Case Western Reserve University, will be partnering with a commercial research and manufacturing firm, Ardiem Medical, on a grant from the U.S. Army’s Telemedicine and Advanced Technology Research Center. The focus of the two-year project is designing a system to allow smoother, more natural control of artificial arms and hands.

The system envisioned by principal investigator Robert Kirsch, PhD, will use implantable electrodes developed previously at the FES Center. Researchers there have pioneered the use of electrodes to stimulate the paralyzed muscles of patients with spinal cord injury or stroke and help restore their ability to walk, stand or grasp objects.

In the new prosthetics project, the electronic sensors will be implanted onto arm and shoulder muscles surrounding the amputation. They’ll pick up electrical currents generated in the brain and sent to the muscles through the nervous system. Kirsch is developing software that will then translate the signals into commands to drive the motors of the prosthesis. So when the user thinks about raising or closing his hand, the device will move accordingly, in a “smooth, fluid and coordinated” manner, says Triolo.

‘Myoelectric’ limbs evolve

The underlying scientific concept is not new—"myoelectric" arms have been around since the 1960s, when researchers first showed they could tap electrical activity in muscles to power artificial limbs. Today’s models are lighter and have longer-lasting batteries, but they are still relatively clunky for users. High-tech advances have come at a faster pace in lower-limb prosthetics, given the larger population of lower-limb amputees.

Kirsch says using an implantable system—rather than sensors that sit on the surface of the skin, as found in most existing myoelectric models—will allow for more electrodes, and thus more control points. It will also avoid complications that arise due to perspiration, inconsistent placement on the body, and electrical static.

The researchers say they’ll be able to integrate their new control system with

see PROSTHETIC on pg. 8
VA system tops private hospitals in infection-control study

A medical centers are more likely than non-VA hospitals to follow recommendations for preventing bloodstream infections associated with central venous catheters, according to a survey of more than 500 U.S. health care centers. The results appear in the June issue of Mayo Clinic Proceedings.

The recommendations were published by the Agency for Healthcare Research and Quality in 2001, and by the Centers for Disease Control in 2002. Since then, “There really had not been any national studies that had looked at whether hospitals were following the recommendations,” said lead author Sarah Krein, PhD, a health-services researcher at the Center for Practice Management and Outcomes Research at the VA Ann Arbor Healthcare System.

The recommendations include:

- Maximal sterile barrier precautions for inserting a central venous catheter. This includes sterile gloves and gown, mask, cap, and a large sterile drape
- Chlorhexidine gluconate (2 percent) on the skin as an antiseptic before insertion, rather than povidone iodine or alcohol
- Replacing catheters as needed, rather than every 4 to 7 days
- Using antimicrobial catheters, but only if other precautions do not reduce infection rates

Krein and colleagues completed a survey of 95 VA and 421 non-VA hospitals in 2005. “Regular use” refers to always, or almost always, using a procedure.

Most hospitals reported regular use of maximal sterile barrier precautions (MSB) to prevent infection: 84 percent of VA hospitals and 71 percent of non-VA hospitals. Ninety-one percent of VA hospitals regularly used chlorhexidine gluconate as an antiseptic, compared with 69 percent of non-VA hospitals.

There were no differences between VA and non-VA hospitals with regard to routine central line changes or antimicrobial catheters.

However, 62 percent of VA hospitals reported regularly using a combined approach of MSB, chlorhexidine gluconate and the avoidance of routine central line changes. Only 44 percent of non-VA hospitals used this combination of techniques.

A central venous catheter (CVC), or central line, is inserted in a vein in the chest to facilitate giving drugs, fluids or nutrition. Some 200,000 CVC-associated bloodstream infections occur each year in the United States, increasing mortality risk, morbidity, and hospital stays and costing some $6 billion.

Compared with non-VA hospitals, VA hospitals responding to the survey had higher RN staffing ratios and were more likely to have an approved residency training program, hospital epidemiologist, and supervisory infection-control professional certified in infection control and epidemiology.

In addition to these advantages, Krein said centralized purchasing could account in part for VA’s edge. She also cited communication within the agency: “Infection control practitioners within the VA have their own website and email list, so there’s a lot of communication there. That could lead to changes in practice.”

VA hospitals were more likely to have approved residency training programs and supervisory professionals certified in infection control and epidemiology.
LIVER (from pg. 1)

in which the liver becomes inflamed and scarred. But people with NASH—probably around 20 or 30 percent of the overall population with fatty liver—can develop advanced scarring, or cirrhosis, and are at higher risk for liver cancer and liver failure. Cirrhosis, marked by fatigue, weight loss, esophageal bleeding and other symptoms, kills some 27,000 Americans per year.

Cusi, an endocrinologist at the San Antonio VA Medical Center and the University of Texas Health Science Center, led a recent study of pioglitazone—a widely prescribed diabetes drug—to treat fatty liver disease. The drug seems to be a “perfect fit,” he says, since it helps insulin resistance and improves blood-sugar control—both major factors in the development of NASH. As of now, the drug, sold as Actos, is approved by the Food and Drug Administration only for diabetes; physicians treating fatty liver disease usually recommend only weight loss.

Diabetes-liver link long overlooked

While it might seem obvious that a diabetes drug could help fatty liver disease, given the shared metabolic underpinnings of the two conditions, the connection had largely been ignored until recently. Cusi explains that while most diabetes patients may in fact have fatty liver, they typically don’t have elevated liver enzymes, which would prompt primary care doctors or endocrinologists to order a biopsy or other tests to check for liver trouble.

It was only through research on other diabetes-related issues that Cusi’s group discovered the liver connection. “We were looking at diabetics for other reasons,” he said, “and we were finding that fatty liver was far more common than we thought.”

The trial his team conducted, funded in part by drug manufacturer Takeda, included 55 men and women. All were overweight or obese, and all had NASH—as confirmed by liver biopsy—plus either diabetes or glucose intolerance, also known as pre-diabetes. Participants cut their calorie intake and were randomized to either pioglitazone or a placebo.

In addition to other measurements, the researchers used magnetic resonance spectroscopy to measure fat in the liver before and after treatment. “It’s the gold standard for examining the amount of fat in the liver,” notes Cusi. “Only a few centers in the U.S. have this available.”

Diabetes drug cuts fat in liver

After six months of treatment, the medication group saw a 54-percent reduction in their liver fat, while the placebo group had no reduction at all. The drug group also saw more favorable results in most other measures, such as insulin sensitivity, glucose metabolism, triglyceride levels and liver inflammation. On the down side, those volunteers taking pioglitazone gained two or three pounds on average—a known side effect of the drug—while the placebo group stayed about the same weight. As long as patients are careful with diet, says Cusi, added weight should be more than offset by the benefits of treatment.

The results appeared in the Nov. 30, 2006, New England Journal of Medicine. Cusi calls the study an “exciting first step,” but points out that the results will need to be replicated in larger trials of longer duration.

Screening study to include up to 250 veterans

Meanwhile, another trial has begun at the Cleveland Clinic and Case Western Reserve University to test the benefits of pioglitazone for fatty liver. And researchers around the world are exploring a variety of other approaches as well, ranging from conventional to alternative: other diabetes drugs, weight-loss surgery, vitamins, essential fatty acids, cinnamon and other herbs. But results so far are preliminary and quite mixed.

For his part, Cusi is securing final approvals for a screening study to involve up to 250 veterans with diabetes. The goal will be to get a better handle on the prevalence of fatty liver disease. The VA researcher points out that his site, San Antonio, with its large Hispanic population, is a “hotbed” for both diabetes and fatty liver disease, and may be an ideal setting in which to learn more about both conditions.

Poor diet leads quickly to fatty liver, diabetes in mice

When Brent Tetri, MD, and colleagues fed a junk-food diet to mice for 16 weeks, it was even sooner than they expected that they saw the signs of fatty liver disease and diabetes.

Tetri’s group at the Saint Louis VA Medical Center and Saint Louis University studied the effects of a diet that was 40 percent fat—typical of fast-food fare—and loaded with high-fructose corn syrup, a sweetener common in soda and some juices. The corn syrup content translated into about eight cans of soda a day in a human diet. Moreover, the mice in the study were allowed only limited physical activity.

“We had a feeling we’d see evidence of fatty liver disease by the end of the study,” said Tetri. “But we were surprised to find how severe the damage was and how quickly it occurred. It took only four weeks for liver enzymes to increase and for glucose intolerance—the beginning of type 2 diabetes—to begin.”

The researchers presented their results at the Digestive Diseases Week meeting in Washington, DC, in late May.
any state-of-the-art artificial upper limb. “We’ll use the motors they have, but rather than use the algorithms they’ve embedded into the system, we’ll come up with our own,” notes Kirsch. “It’ll look the same to the user, but it will feel different in terms of how they control it.”

Triolo offers the analogy of replacing a car’s manual transmission with an automatic one. “We’re not touching the motor—we’re changing how the driver interacts with the motor.”

In a second phase of the Army-funded project, APT Center engineer Dustin Tyler, PhD, will test an electrode that will be housed inside the prosthesis and sense its position and grip strength. That feedback will give users the sensation they need to use the hand more naturally. Kirsch: “There’s a lot of evidence that performance in tasks is improved if the user has sensation. The control system performs better when there’s more feedback.”

Adds Triolo, “If the user can get some sense of where the machine is without having to concentrate on it, that’s a big plus.”

VA audiology-research center selected to host NIH-funded training

The National Center for Rehabilitative Auditory Research (NCRAR), located at the Portland VA Medical Center, is one of three sites selected by the National Institute of Deafness and Communication Disorders to host a new summer research training program for doctoral students in audiology. Each summer for at least the next five years, students will spend three months at NCRAR receiving training in research ethics and methodology and working alongside established audiology investigators on clinical studies in areas such as tinnitus and hearing loss. ■

(From left) Gabrielle Saunders, PhD, of VA’s Portland-based National Center for Rehabilitative Auditory Research, instructs audiology students Kelly Watts and Justin Howell in the center’s anechoic chamber.