

Robot-assisted stroke therapy to be tested at four VAMCs

Therapy that uses robots to help chronic stroke patients move their affected upper limbs will be compared with intensive non-robotic therapy in a new VA clinical trial involving 158 veterans at the West Haven, Seattle, Gainesville and Baltimore VA medical centers.

The trial, which kicked off last month, is the first to be funded jointly by VA's Rehabilitation Research and Development Service and its Cooperative Studies Program. The chairperson is Albert Lo, MD, PhD, of West Haven.

The study will feature a robot called the MIT-Manus, developed at the Massachusetts Institute of Technology. Patients sit at a table with their affected arm attached to the robot. They follow prompts on the screen—or instructions from a therapist—and try to perform a task with their arm. The robot senses their movement and helps as needed.

'Power steering' for the arms

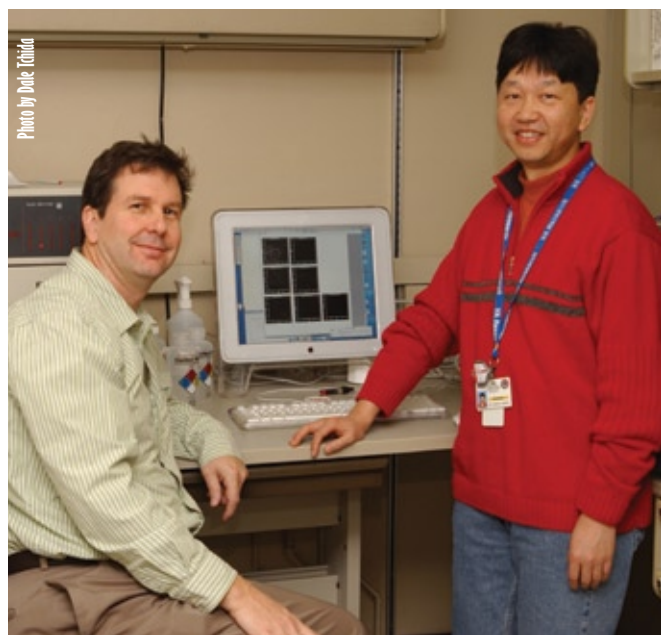
"These are videogame-like tasks," said neurologist George Wittenberg, MD, PhD, principal investigator for the Baltimore site. "The patients are moving a cursor from one place to another, or guiding a symbol on the screen through a maze, and using their arms to control the movement of the cursor. The robots provide 'power steering' for the arms—just enough assistance to allow people to move."

Adds Wittenberg: "The design of the robotic therapy, in at least some of the control paradigms, actually mimics what therapists do—the so-called hand-over-hand therapy, where the therapist is asking the person to move, but then provides assistance and support where needed. The difference has to do with the intensity and the duration of therapy that's possible with the robot."

The goal is to help restore motor function. In previous research with the robots, patients produced "short, fragmentary movements," said Wittenberg, that over time became longer and smoother. In one study, patients in the robot-assisted group improved twice as much as those in the usual-care group.

The therapy relies on neuroplasticity—the ability of the adult brain to "rewire" itself. When neurons die because of a stroke, other brain cells—prompted by assisted body movements—apparently begin compensating for the lost function. Researchers have been working to identify the best therapies to exploit this phenomenon, and find out how long after a stroke it remains active.

see **ROBOT** on pg. 8



Jack Stapleton, MD (left), and Jinhua Xiang, MD, of the Iowa City VAMC.

Study probes virus that blocks HIV

Researchers at the Iowa City VA Medical Center and University of Iowa have new insight on how a seemingly harmless virus called GBV-C may prolong life for patients infected with HIV. In a study published online this month in the *Proceedings of the National Academy of Sciences*, the investigators identified a segment within a protein manufactured by GBV-C that strongly inhibits HIV from growing in cell models.

see **VIRUS** on pg. 6

Update from Rehabilitation Research and Development

Tinnitus among research priorities at Portland center of excellence

By Patricia A. Dorn, PhD, assistant director and acting deputy director

For nearly 10 years, RR&D's National Center for Rehabilitative Auditory Research (NCRAR), based at the Portland VAMC, has been one of the nation's premier sites for audiology research. On the occasion of the center's recent dedication of its expanded clinical research space, we'd like to draw attention to one particularly critical and timely area of investigation at this site.

Tinnitus is the persistent perception of sound that does not have a source outside of the head. It has been referred to as "phantom auditory perception." The condition is symptomatic of auditory dysfunction, and is not a disease in itself. Like pain, tinnitus is a subjective experience that can be described only by patient report.

Epidemiological studies reveal that tinnitus affects from 10 to 15 percent of adults, or some 40 million Americans. Fortunately, most people who experience tinnitus are not significantly bothered by it. For many, however—some 5 to 13 million Americans—the condition is clinically significant and can disrupt their ability to communicate and function effectively throughout the day.

Tinnitus is more common in men than in women and tends to increase with advanc-



Marking the opening this past summer of a new 21,000-square-foot clinical research facility at the National Center for Rehabilitative Auditory Research were (from left) Portland VAMC director James Tuchsmidt, MD; VA chief research and development officer Joel Kupersmith, MD; and NCRAR director Stephen Fausti, PhD.

ing age. It is estimated that 3 to 4 million of our nation's 25 million veterans experience chronic tinnitus, of whom up to 1 million require some degree of clinical intervention. These estimates are based on epidemiological data from the general population; the actual numbers may be higher for veterans because of their higher average age and greater noise exposure. Indeed, tinnitus is one of the most common disabilities among current veterans, and may affect veterans of operations Iraqi Freedom and Enduring Freedom as well.

James Henry, PhD, a research career scientist at NCRAR, has developed a research program to address clinical needs related to tinnitus. Dr. Henry notes that a major challenge with tinnitus is accurate diagnosis, which is important to ensure proper treatment and prevent unnecessary costs to the VA. One of the program objectives is to develop computer-automated tinnitus

assessment procedures that can be used in a standardized fashion. Individuals with and without tinnitus have been tested using the automated techniques. Preliminary data reveal significant differences in responses between groups. One objective of the work is to develop and document a defined test for detecting the presence or absence of tinnitus with a high degree of confidence. Dr. Henry's work has also resulted in the development of a progressive intervention model of tinnitus management that will be useful in treating veterans with tinnitus at all levels of need.

For more information on the NCRAR and Dr. Henry's tinnitus research program, go to www.ncrar.research.va.gov.

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Study suggests current LDL treatment goals based on flawed trials

While the use of statin drugs to cut cardiovascular risk is supported by solid clinical evidence, commonly recommended treatment targets for low-density lipoprotein (LDL) cholesterol—so-called “bad cholesterol”—are based on faulty science, say investigators at VA’s Center for Practice Management and Outcomes Research in Ann Arbor. They reported their findings in the Oct. 3 *Annals of Internal Medicine*.

The researchers, led by center director Rodney Hayward, MD, analyzed hundreds of controlled trials, cohort studies and case-control studies that examined the independent relationship between LDL cholesterol and major cardiovascular outcomes—such as heart attack or stroke—in patients with LDL levels under 130 mg/dL.

“Our research suggests that low LDL-C targets frequently proposed in practice guidelines are based on flawed epidemiology,” said Hayward.

He stressed: “We want to make clear that this research does not mean that the LDL targets are necessarily wrong, only that there is no valid clinical evidence to support them. The paper is merely proving that the science that is commonly believed to support the current LDL targets has fundamental errors and it is essential that we go back and repeat these analyses correctly before we can know if the LDL recommendations are a clinical sensible approach.”

Current treatment guidelines, published in 2004 by an expert panel affiliated with the federal National Cholesterol Education Program (NCEP) and backed by organizations such as the American Heart Association and American Diabetes Association, urge physicians to adjust lipid therapy to achieve LDL levels of less than 70 mg/dL for patients at very high cardiovascular risk, and less than 100 mg/dL for those at high risk.

According to Hayward and colleagues, it is unclear from the literature whether LDL reduction is “truly the dominant beneficial mechanism of statin therapy.” They say little evidence exists to show that adding additional drugs for those already on lipid-lowering medication, in an effort to drop their LDL to the recommended levels, is beneficial or safe.

“Titration of lipid therapy to recommended LDL cholesterol goals entails considerably greater clinical complexity, frequent use of multidrug therapy, and greater societal and patient out-of-pocket costs,” wrote the authors, and in some cases could “result in net harm to patients.”

The study, which was reported on by the *New York Times*, included the following findings:



Photo by Mike Hormuth

Rodney Hayward, MD, and colleagues at VA’s Center for Practice Management and Outcomes Research in Ann Arbor analyzed hundreds of studies on LDL cholesterol and found “no high-quality clinical evidence to support currently proposed treatment goals.”

- Although there is clear and compelling evidence to support the use of at least a moderate dose of statins for high-risk heart patients—if tolerated—no high-quality evidence shows that the dose should be adjusted to reach the recommended LDL targets.
- Journal articles reviewed by Hayward’s team often advocated for tight LDL control without discussing possible risks, patient burden, and the costs to society.
- Studies addressing the benefits of reaching LDL goals were marked by avoidable problems such as relying on aggregate analyses and ignoring statins’ other proposed mechanisms.

Other research flaws encountered by Hayward’s group: “mistaking cohort analyses for true experimental results”; failing to control for exposure to treatment in cohort analyses that use clinical trial data; and “framing treatment goals as false dichotomies.”

According to the VA authors, researchers with access to the data they reviewed should conduct further analyses, keeping in mind

see **LDL** on pg. 7

The rich history of VA research

Tackling tuberculosis after World War II: The streptomycin trial

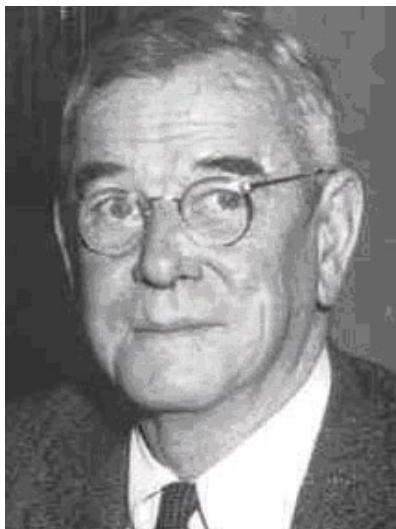
Editor's note: The following account is based on an excerpt from "VA Research, 1925 – 1980," a history compiled by Dr. Marguerite Hays, who directed VA's Medical Research Service from 1974 – 1979 and the overall VA research program from 1979 – 1981. The complete, fully referenced text is expected to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

After World War II, one of the first problems General Paul Hawley tackled as head of VA's medical department was the needs of the new veterans who had tuberculosis. At that time, some 12,000 veterans were hospitalized in VA hospitals for tuberculosis, and their number was growing steadily.

Hawley persuaded Dr. John Barnwell, a professor at the University of Michigan, to come to Washington to lead the VA fight against tuberculosis. Barnwell was a well-known authority on the disease, who himself had been treated for tuberculosis. Equally important, he was active in the American Trudeau Society (a non-government organization advocating tuberculosis research) and a personal friend of leaders in the field. His goal was to use every resource available to him to improve the care of the tuberculous veteran. ...

Streptomycin initially greeted with skepticism

For half a century, since Robert Koch's discovery of the tubercle bacillus as the cause of tuberculosis, attempts at systemic treatment had been made. These treatment approaches began with Koch's own



John Barnwell, MD

enthusiastic, but eventually disappointing, use of tuberculin, an inactivated product of the tubercle bacillus, and ranged through the use of sanocrysin, a gold compound, in the 1920s and 1930s. A study that may have been the first placebo-controlled clinical trial in the world proved sanocrysin to be disappointingly ineffective in curing tuberculosis. Transient enthusiasms occurred for proposed cures, only to prove ineffective. An example is the use of turtle serum, thought to be effective because the turtle has antibodies to a type of mycobacterial disease. One disappointment after another led to a pervading skepticism about any proposed new treatment for this persistent and resistant disease. When streptomycin was discovered in 1944, appearing in the wake of penicillin's spectacular wartime success, it was greeted with suspicion by the older, more experienced, phthisiologists. ...

Streptomycin was known to inhibit the tubercle bacillus in culture. But despite a few isolated cases successfully treated, no one really knew if clinical tuberculosis

would be helped by streptomycin. ... Barnwell, chair of a "Streptomycin Committee" appointed by General Hawley, and the group's secretary, Dr. Arthur Walker, set out to try to answer that question.

Trial modeled after wartime penicillin studies

Walker had been a part of the central group coordinating the wartime studies of penicillin treatment of syphilis. Those studies depended on systematic study of the patient before and during treatment, standardization of a prescribed regimen of treatment, and adequate follow-up. Comparison with an untreated control series of patients, or with patients treated with the then-standard arsenical and bismuth regimens, was not a part of these studies. Instead, the investigators drew on their significant personal clinical knowledge about the natural history of syphilis, knowledge believed sufficient to predict the course the disease would have without penicillin.

The design for the first VA-Armed Forces study of streptomycin in tuberculosis, begun in 1946, followed the same pattern as that used for the study of penicillin in syphilis: carefully defined study of the patient before treatment; prediction of what the patient's clinical course would be without treatment; standardization of treatment to a single dosage schedule; observation for the effect of treatment on signs and symptoms of tuberculosis; repeated cultures to isolate the tubercle bacillus; observation for treatment complications; and post-treatment follow-up.

see **STREPTOMYCIN** on pg. 5

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.

“The ACTIVE Cognitive Training Trial and Health-Related Quality of Life: Protection That Lasts for Five Years.” Fredric D. Wolinsky, PhD. **Iowa City.** *Journal of Gerontology Series B: Psychological Sciences and Social Sciences*, Sept. 2006.

“Antibiotic Therapy and 48-Hour Mortality for Patients with Pneumonia.” Eric M. Mortensen, MD, MSc; Marco I. Restrepo, MD; Antonio Anzueto, MD; Jacqueline A. Pugh, MD. **San Antonio.** *American Journal of Medicine*, Oct. 2006.

“Associations of Race with Depression and Symptoms in Patients on Maintenance Hemodialysis.” Steven D. Weisbord, MD, MSc; Linda F. Fried, MD, MPH; Galen E. Switzer, PhD; Michael J. Fine, MD, MSc. **Pittsburgh.** *Nephrology Dialysis Transplantation*, Sept. 23, 2006 (Epub).

“Correlates of Depressive Symptoms among Women Seeking Cancer Genetic Counseling and Risk Assessment at a High-Risk Cancer Clinic.” Molly Kodl, PhD, **Minneapolis.** *Journal of Genetic Counseling*, Aug. 2006.

“Determining Predictors of Delayed Recovery and the Need for Transitional Cardiac Rehabilitation After Cardiac Surgery.” Jane A. Anderson, MSN, RN; Nancy J. Petersen, PhD; Pamela Willson, PhD, RN. **Houston.** *Journal of American Academy of Nurse Practitioners*, Aug. 2006.

“Direct Reporting of Laboratory Test Results to Patients by Mail to Enhance Patient Safety.” Valerie Forman-Hoffman, PhD, MPH. **Iowa City.** *Journal of General Internal Medicine*, Oct. 2006.

“The Effect of Donepezil on Memory in Older Normal Subjects.” David B. Fitzgerald, MD; Gregory P. Crucian, PhD; Kenneth M. Heilman, MD. **Gainesville.** 1st Florida Residents and Fellows Research Day and Fellowship Conference, Sept. 23, 2006.

“Elderly Veterans’ Beliefs Concerning Life-Sustaining Treatment and the Control of Their End-of-Life Health and Health Care.” Keri L. Rodriguez, PhD. **Pittsburgh.** *Journal of Aging and Health*, Oct. 2006.

“Functional Recovery in T13 SCI Rats Resulting from Peripheral Nerve Rerouting: Role of the CNS Neuroplasticity.” **Boston.** 2006 Congress of Neurological Surgeons Annual Meeting, Oct. 7-10, 2006.

“Glycosylated Hemoglobin Level and Development of Mild Cognitive Impairment or Dementia in Older Women.” Kristine Yaffe, MD. **San Francisco.** *Journal of Nutrition, Health and Aging*, July/Aug. 2006.

“Maribavir Sensitivity of Cytomegalovirus Isolates Resistant to Ganciclovir, Cidofovir or Foscarnet.” Gail I. Marousek, BS; Sunwen Chou, MD. **Portland.** *Journal of Clinical Virology*, Sept. 7, 2006 (Epub).

“Mental Status after West Nile Virus Infection.” Kathleen Y. Haaland, PhD; Joseph Sadek, MD; Larry D. Davis, MD; Joanne Harnar. **Albuquerque.** *Emerging Infectious Disease*, Aug. 2006.

“Neuropsychological Function and Delay Discounting in Methamphetamine-Dependent Individuals.” William F. Hoffman, MD, PhD; Raymond Templin, PhD; Robert J. Hitzemann, PhD. **Portland.** *Psychopharmacology*, Oct. 2006.

“Predictive Value of a Positive Fecal Occult Blood Test Increases as the Severity of CKD Worsens.” Edmund J. Bini, MD, MPH; David S. Goldfarb, MD. **New York.** *American Journal of Kidney Diseases*, Oct. 2006.

“Prospective Comparison of Patient Experience with Colon Imaging Tests.” Hayden B. Bosworth, PhD; Linda L. Sanders, MPH; Jim Henderson, MD; Edmund J. Bini, MD; Don C. Rockey, MD; Judy Yee, MD; Kenneth McQuaid, MD. **New York, Durham, San Francisco.** *American Journal of Medicine*, Sept. 2006.

“Socioeconomic Determinants of Planned Methadone Treatment.” Aram Dobalian, PhD, MPH. **Sepulveda.** *American Journal of Health Behavior*, Sept./Oct. 2006.

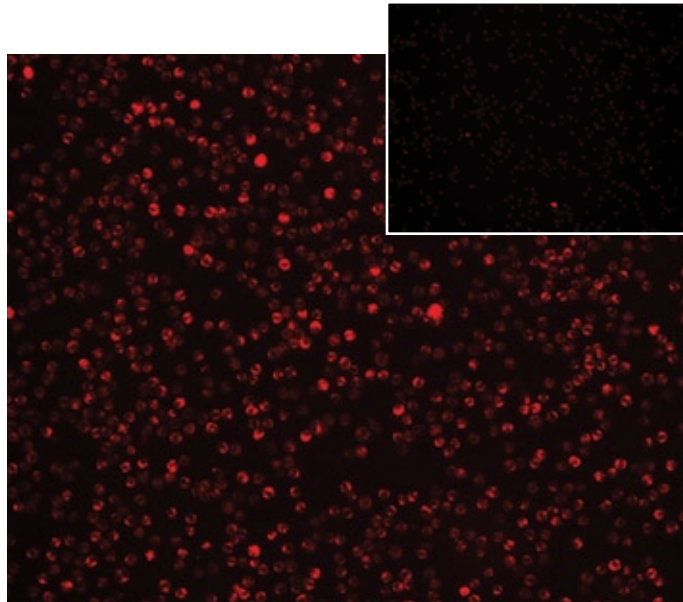
“Surface Electromyography Activity of Trunk Muscles During Wheelchair Propulsion.” Alicia M. Koontz, PhD; Ronald J. Triolo, PhD; Michael L. Boninger, MD. **Pittsburgh, Cleveland.** *Clinical Biomechanics*, Sept. 14, 2006 (Epub).

“Tobacco Cessation Counseling Across the Ages.” Amy E. Wallace, MD, MPH; William B. Weeks, MD, MBA. **White River Junction.** *Journal of American Geriatrics Society*, Sept. 2006. ■

STREPTOMYCIN (from pg. 4)

In their first report to the AMA Council on Pharmacy and Therapeutics, Barnwell and Walker cited the preliminary reports about streptomycin, especially those already published from the Mayo Clinic. The reports made clear that the widespread VA-Armed Forces clinical study was founded on good evidence that streptomycin was effective in at least some instances. ■

Human-derived immune cells that express a protein called NS5A (seen in larger slide), made by a virus known as GBV-C, slow the growth of HIV, as compared with control cells that do not express the protein (inset). The exact mechanism by which NS5A works is under investigation by a team at the Iowa City VAMC, and may one day lead to new therapies for HIV.



VIRUS (from pg. 1)

Lead author Jinhua Xiang, MD, and senior author Jack Stapleton, MD, conducted their experiment as a follow-up to previous clinical research—by their team and others—showing that HIV patients who also are infected with GBV-C live longer than those infected only with HIV.

“Identifying a specific protein made by GBV-C that inhibits HIV growth in cell culture strengthens the argument that GBV-C is responsible for the prolonged survival observed in several studies of HIV-positive people,” Xiang said. “Understanding how the protein works may allow us to develop target-specific therapies that can mimic these effects and inhibit HIV.”

Xiang added: “Potentially, these novel therapies would have certain advantages over current drugs, as the newer therapies would target the cell in which HIV can replicate and not the virus directly. Therefore, HIV should have more difficulty developing resistance to the effects of this protein.”

Xiang previously discovered that GBV-C grows in the same type of white blood cell,

the CD4 T-cell, that harbors HIV when it enters the body. HIV attaches to this T-cell by first landing on the CD4 receptor. After it binds with the receptor—a molecular “docking site”—HIV enters the cell and disrupts its functioning. This eventually leads to a depletion of these cells and results in immune deficiency syndrome, or AIDS.

“People with GBV-C have a slower rate of destruction of these T-cells,” noted Stapleton, who directs the division of infectious diseases at the Iowa City VA and the University of Iowa.

The new lab study identified a protein called NS5A, a product of GBV-C, and homed in on an 85-amino-acid segment of the protein that appears to inhibit HIV—in part, by decreasing the number of CD4 receptors available to the AIDS virus.

Further protein-mapping needed

Xiang cautioned that more research is needed to understand more fully the actions of the NS5A protein. The goal is now to systematically strip away more and more of the protein and to identify the smallest possible fragment responsible for HIV inhibition.

“Before NS5A can be used for any kind of therapy, we need to further map it,” explained Xiang. “We need to zero in to see what region has the critical effect on HIV inhibition.” The team will then seek to develop small-molecule drugs that mimic the inhibiting action.

Stapleton noted that GBV-C is nontoxic to T-cells and not associated with any human disease. As a result, the U.S. Food and Drug Administration does not require that blood donations be screened for this common virus, even though up to three percent of healthy blood donors in the U.S. have active GBV-C infection. An additional 12 percent have antibodies at the time of donation, indicating past exposure.

A ‘strange story’

Stapleton and Xiang first began studying the GBV-C and HIV connection because they were skeptical of earlier studies published in the mid-1990s.

“It was a strange story,” Stapleton said. “Who would have thought that there was a virus floating around in a lot of people that does not make them sick, but that could significantly influence the course of their HIV infection?”

Stapleton and Xiang conducted an initial clinical study that found that HIV patients who were co-infected with GBV-C the day they walked in the clinic door tended to live more than three times longer than those who were not co-infected with GBV-C. The study was published in 2001 in *The New England Journal of Medicine*.

In addition to Stapleton and Xiang, researchers on the new study included James McLinden, PhD, Qing Chang, and Thomas Kaufman. The research was funded by VA and the National Institute of Allergy and Infectious Diseases. ■

Methodology moments...

The challenge of establishing causation

Editor's note: 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. The overall mission of the Seattle ERIC is to improve the health and health care of veterans by promoting the principles and practice of state-of-the-art epidemiologic research within the Veterans Health Administration.

For many of us in the health sciences, the ultimate goal of scientific inquiry is to describe the underlying causal pathways that link genetics, biology, environment, and human systems to physical and mental health and to use this understanding to prevent or cure disease. Determining causality in experimental and non-experimental observational research can be challenging and demands rigorous methodologies.

The gold standard: randomized controlled trials

Randomized controlled trials are experiments and the gold-standard for inferring causality. Although useful in many medical settings, this approach is often limited by feasibility issues or ethical concerns.

In the absence of randomization, other approaches have been conceptualized. In 1965, Sir Austin Bradford Hill proposed a seminal set of guidelines for assessing causality that are still widely used. The guidelines include: strength of the association, where stronger associations are more supportive of causality; consistency of the association, where the association is observed repeatedly across time, locations, and populations; temporality, where cause precedes effect; biologic gradient or dose-response, where more exposure is associated with more effect; biologic plausibility, where observed association fits biologic models from the laboratory; and experimental evidence, where manipulation of the exposure changes the outcome.

'Factuals' and 'counterfactuals'

More contemporary efforts to clarify thinking about causal inference have relied upon the use of factuals and counterfactuals, also known as "potential outcomes." Most simply this concept argues that for a person who is exposed to A and then experiences outcome B, A is considered causal if and only if, had that same person not been exposed to A, she/he would not have experienced outcome B.

At issue is that a person cannot simultaneously be exposed and not exposed to A. Hence the observed association of exposure A and outcome B, the factual, must be compared to an unobservable situation, the counterfactual, where exposure A does not occur yet all other factors are identical. Although it is not practical to compare factuals with counterfactuals, the approach can be informative when planning a study and readily understood when thinking about the role of randomization in the experimental process: the creation of 2 or more groups that differ only in terms of an exposure.

Obituaries

Linda Quade, administrator at Mountain Home

Linda M. Quade, administrative officer for research and development at the Mountain Home, Tenn., VA Medical Center, was killed in a traffic accident on her way to work on Sept. 14. Quade, 60, had been with the research service at Mountain Home more than 16 years, and, according to George Youngberg, MD, associate chief of staff for research at Mountain Home, was instrumental in helping the site attain accreditation for its research program.

James Rowan, led VA study on older epileptics

A. James Rowan, MD, chief of neurology at the Bronx VAMC and a neurologist at Mount Sinai Medical Center, died of lung cancer on Aug. 27 at the age of 71. An expert on epilepsy, Rowan had chaired a multisite VA clinical trial comparing three medications for the condition in older patients. The results were published in *Neurology* in 2004. Rowan was also noted for his teaching and research on using electroencephalography, or EEG, to identify brain abnormalities associated with epilepsy.

LDL (from pg. 3)

the methodological pitfalls pointed out in their article. For example, they wrote, "Much more reliable evidence on currently proposed LDL cholesterol goals could be expeditiously produced by conducting cohort analyses of past statin trials that control for statin dose and pill adherence."

Said Hayward, "Our paper lays out how this type of epidemiology—assessing the relative merit of recommended treatment targets—should be done correctly in the future."

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ROBOT (from pg. 1)

“The older thinking was that approximately a year after a stroke, there wasn’t any useful neuroplasticity and that further therapy wouldn’t have any further effects on motor function,” noted Wittenberg. “But there have now been several studies using a variety of techniques that have shown gains after that one-year time period, and there is evidence that there is plasticity that still goes on long after a stroke.”

Participants in the new study will be at least six months post-stroke, and will receive 12 to 14 weeks of therapy, one hour three times per week. In the non-robotic arm of the study, therapists will help patients with stretching, guided reaching, and other activities to achieve the same functional goals as those using the robots. In real-world practice, patients at this stage after a stroke are typically receiving little, if any, formal therapy.

If the robots shine in the new VA study, they could be well on their way to becoming a regular part of stroke therapy in clinics across the nation. According to study



Sharon Turner, a patient at the Baltimore VA Medical Center, receives therapy with the MIT Manus.

chairman Lo, “If robotic training proves beneficial, it will make more widely available high-quality, evidence-based rehabilitative care at a time when there is a shortage of experienced therapists and a progressively growing rehabilitative need for veterans and all Americans.” ■

To report upcoming publications and presentations to R&D Communications, see:
www.research.va.gov/resources/policies/pub_notice.cfm