

VA RESEARCH & DEVELOPMENT



IMPACTS 2002—2003

Impacts 2002-2003 was produced by VA Research and Development Communications in Baltimore, Maryland in collaboration with the VA Office of Research and Development Biomedical Laboratory R&D Service, Clinical Science R&D Service, Rehabilitation R&D Service, and Health Services R&D Service. Additional information about VA Research and Development activities is available on the World Wide Web at:

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August 2004

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VA RESEARCH IMPACTS FOR 2002-2003

GENERAL OVERVIEW



The four services of the Department of Veterans Affairs (VA) research program together cover a spectrum of scientific research, including basic biomedicine, clinical science, rehabilitation, and health services research. One way the Office of Research and Development (ORD) provides synergy to these efforts is by organizing the research enterprise into research areas that cut across traditional research boundaries and represent health issues of concern to the veteran population. While pursuing the common goal of improving health care for veterans and the nation, each service brings unique strengths to our endeavor.

Increasingly, our services find common interests and opportunities for collaboration across medical disciplines. Even as each service conducts research within their own specialties, they are bound by the unifying goal to ensure that our veterans receive the best possible care. More than ever, the priority of ORD is to connect the impact of our research findings to patient care. This document highlights some of VA's recent research accomplishments and I am pleased to share them with you.

Stephan D. Fihn, MD, MPH
Acting Chief Research & Development Officer

Biomedical Laboratory Research and Development



VA Biomedical Laboratory Research and Development Service (BLR&D) has played a major role in the Office of Research and Development's history of serving veterans and the United States as a whole. Its exciting achievements in basic and clinical research frequently lay the groundwork for improved patient care.

In 1998, Ferid Murad, MD, PhD, shared the Nobel Prize in Medicine in part for his research results at the Palo Alto VA Medical Center that were instrumental in illuminating the role of nitric oxide in body functions including the relaxing of blood vessels and regulation of blood pressure. In 1977, the Nobel Prize for Medicine was shared by two VA scientists – Rosalyn Yalow, PhD, of the Bronx VA Medical Center, and Andrew Schally, PhD, of the New Orleans VA Medical Center. Dr. Yalow's work with radioisotopes formed the basis for modern routine diagnostic assays that use radioactive materials; Dr. Schally was honored for key discoveries on the workings of the endocrine system.

Contributions of BLR&D also include many other landmark advances, such as the successful treatment for tuberculosis, the first successful liver and kidney transplants, the concept that led to the development of the CAT scan, drugs for treatment of mental illnesses, and the development of the cardiac pacemaker. Notable recent discoveries include identification of genes linked to Alzheimer's disease and schizophrenia, new treatment targets and strategies for substance abuse and chronic pain, and potential genetic therapy for heart disease.

Following are highlights of some recent accomplishments by our scientists, including their publication citations or project identification numbers.

Timothy J. O'Leary, MD, PhD
Director

1. HORMONE REVEALS UNEXPECTED SKELETON-BOLSTERING POWER

A hormone renowned for goading the thyroid gland now reveals a talent for restraining bone destruction, according to the recent finding reported by VA osteoporosis researchers. The study uncovers an unexpected reason why an overactive thyroid triggers osteoporosis, and it could lead researchers to novel bone-boosting drugs.

To keep the skeleton healthy, cells called osteoclasts break down old bone and cells known as osteoblasts. However, once osteoclasts outpace osteoblasts, it results in osteoporosis, a skeleton-weakening disease. It occurs in women due to estrogen loss after menopause and in both genders because of other age-related factors. Hoping to discover ways to maintain bone strength, researchers are striving to understand the balance between the two cells' activities, and they are gaining clues. For instance, osteoporosis occurs in people with hyperactive thyroid glands. Researchers conjectured that too much thyroid hormone spurs bone loss. Another hormone—released by the pituitary gland called thyroid-stimulating hormone (TSH)—prods the thyroid to release thyroid hormone. People with overactive thyroids exhibit low TSH concentrations because thyroid hormone loops back to the pituitary gland and shuts down TSH production. The results of this study indicate that low TSH, rather than excess thyroid hormone, might weaken bone structure.

Bronx and Pittsburgh VA Medical Centers

Abe E, Mariani RC, Yu W, Wu XB, Ando T, Li Y, Iqbal J, Eldeiry L, Rajendren G, Blair HC, Davies TF, Zaidi M. TSH is a negative regulator of skeletal remodeling. Cell. Oct 17, 2003; 115(2):129-30.

2. WARDING OFF DIABETES

Type 2 diabetes is a multifaceted disease. The main causes of Type 2 are insulin resistance, in which the body does not use insulin efficiently; and insulin deficiency, in which the pancreas

cannot keep up with the body's demand for insulin. These conditions can be brought on by obesity, advancing age, and heredity. Recent studies conducted under the diabetes prevention program by VA researchers have shown that physical activity and losing body weight can cut the risk of developing type 2 diabetes significantly. Their studies suggest that obesity-related insulin resistance represents a complex syndrome, mediated by a number of adipocyte secretory products, which ultimately lead to a defect in insulin action in other target organs.

Little Rock VA Medical Center

Kern PA, Di Gregorio GB, Lu T, Rassouli N, Ranganathan G. Adiponectin expression from human adipose tissue: Relation to obesity, insulin resistance, and tumor necrosis factor-alpha expression. Diabetes. Jul 2003; 52:1770-85.

Kern PA, Ranganathan S, Li C, Wood L, Ranganathan G. Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance. Am J Physiol Endocrinol Metab. May 2001; 280:E745-51.

Wang H, Chu WS, Lu T, Hasstedt SJ, Kern PA, Elbein SC. Uncoupling protein-2 polymorphisms in type 2 diabetes, obesity, and insulin secretion. Am J Physiol Endocrinol Metab. Jan 2004; 286:E1-7.

3. SUPPRESSING ARTHRITIS

Susceptibility to rheumatoid arthritis (RA) is strongly associated with expression of specific major histocompatibility (molecules responsible for compatibility) genes called HLA-DR, including DR1 and DR4, in humans. A research team has identified a collagen peptide capable of altering the immune response to type II collagen and suppressing collagen-induced arthritis (CIA) in HLA-DR1 in transgenic mice. The effect of the peptide is mediated, at least in part by IL-4. These experiments represent the first description of an analog peptide of type II collagen recognized by T cells in the context of a human major histocompatibility complex molecule that can suppress autoimmune arthritis. Results from

this study suggest a new mode of therapy for RA in humans.

Memphis VA Medical Center

Dr. Kang received the prestigious VA Middleton Award for outstanding achievement in biomedical research for 2003. The CIA mouse model for arthritis was originally developed by Dr. Kang and has been used worldwide as a model for RA and other autoimmune diseases.

Brand DD, Kang AH, Rosloniec EF. Immunopathogenesis of collagen arthritis. Springer Semin. Immunopathol. 25(1):3-18, 2003.

Myers LK, Sakurai Y, Tang B, He X, Rosloniec EF, Stuart JM, Kang AH. Peptide-induced suppression of collagen-induced arthritis in HLA-DRI transgenic mice. Arthritis Rheumatol. Dec 2002;46(12):3369-77.

4. VARIATION IN GENE TAMES MALARIA

Malaria kills about a million people each year. The risk for contracting the disease is not the same for everyone and some people have a remarkable ability to suppress the debilitating effects of the malarial parasite. Studies led by Dr. Brice Weinberg at the Durham VA Medical Center have tied that resistance with a small variation in a single gene that can cut the risk of developing a life-threatening infection by nearly 90%. The variation (mutation) in the gene results in enhanced production of nitric oxide (NO), a gas that plays a role in diverse physiological processes. This study is very compelling because it demonstrates a connection between genetics, nitric oxide production and clinical status of people infected with the malarial parasite.

Durham VA Medical Center

This study was cited as News of the Week in Science, November 2002; 298(5997), 1317-9.

5. POTENTIAL NEW TREATMENTS FOR PARKINSON'S DISEASE

One of the newest areas in Parkinson's disease research is the investigation of glutamate, a nerve cell transmitter, and its interactions with dopamine in the development of Parkinson's

disease. Researchers have presented preliminary data that several aspects of glutamate metabolism are altered in animal models of Parkinson's disease. Several classes of glutamate receptor activators and inhibitors have been identified as potential new treatments for Parkinson's disease. This work will lay the foundation for the development of entirely new classes of drugs for the treatment of Parkinson's disease.

Ann Arbor, Miami and Portland VA Medical Centers

Kearney JA, Albin RL. mGluRs: a target for pharmacotherapy in Parkinson disease. Experimental Neurology 2003; 184 (Suppl 1):S30-6.

Rama Rao KV, Jayakumar AR, Norenberg MD. Induction of the mitochondrial permeability transition in cultured astrocytes by glutamine. Neurochemistry International 2003; 43(4-5):517-23.

Tompson KW, Suchomelova LM. Transplants of cells engineered to produce GABA suppress spontaneous seizures. Epilepsia 2004; 45(1):4-12.

6. LINK IN EMBRYONIC DEVELOPMENT AND CANCER TREATMENT

VA researchers have identified a surprising molecular link between two mammalian proteins of very different types. The report, published in the journal *Science* with an illustration of the work on the cover page, revealed that a protein whose major function is to help maintain the structure of a cell and a protein responsible for sending communication signals through a cell are interrelated in an unexpected way. This finding may have broad implications for human diseases as it leads to new avenues of research aimed at understanding how different organs develop and may even suggest new ways to approach the treatment of cancer. It is highly possible that certain diseases could arise through mutations that alter the types of interactions highlighted by these studies.

Washington VA Medical Center

Tang Y, Katuri V, Dillner A, Mishra B, Deng CX, Mishra L. Disruption of TGF-beta signaling in ELF beta-spectrin-deficient mice. *Science* Jan 2003; 299, 574-7.

7. NEW APPROACHES FOR TREATMENT OF PROSTATE CANCER

Dr. Andrew Schally, a 1977 Nobel Laureate in medicine and a distinguished investigator at the New Orleans VA Medical Center, is continuing his pioneering work on the development of new hormone-based treatments for advanced prostate cancer (PCA). Dr. Schally introduced the preferred treatment method for men with advanced PCA, which is based on the use of analogous compounds (analogs) to a hormone termed Luteinizing Hormone Releasing Hormone (LHRH). LHRH analogs inhibit PCA by creating a state of sex hormone deficiency (required for cancer growth) and are used for treatment of androgen dependent PCA (a steroid hormone that develops and maintains masculine characteristics). However, for androgen-independent PCA, no effective therapy is currently present. Improved hormone therapy is now being examined for androgen dependent and independent PCA that is based on the use of LHRH analogs alone or in combination with other hormones/peptides. An evaluation of the usefulness of certain analogs of LHRH for chemotherapy targeted to PCA cells that results in less toxic side effects is ongoing. This work is providing important information that can be applied to the prevention of relapse in patients receiving androgen-deprivation therapy, as well as treatment of cancer types for which present therapy is inadequate.

New Orleans VA Medical Center

Letsch M, Schally AV, Szepeshazi K, Halmos G, Nagy A. Preclinical evaluation of targeted cytotoxic luteinizing hormone-releasing hormone analogue AN-152 in androgen-sensitive and insensitive prostate cancers. *Clin Cancer Res.* Oct 2003; 1;9(12):4505-13.

Schally AV, Comaru-Schally AM, Plonowski A, Nagy A, Halmos G, Rekasi Z. Peptide analogs in the therapy of prostate cancer. *Prostate* 2000; 45, 158-66.

8. NEW TECHNIQUES IN THE EARLY DETECTION AND TREATMENT OF PANCREATIC CANCER

Dr. Matthew R. Pincus and colleagues at the Brooklyn VA Medical Center have developed two new peptide drugs against pancreatic (and many other types of) cancer cells. The first drug, PNC-28, kills many different forms of human cancer cells and blocks tumor growth in mice. It has no effect on normally growing cells, including human stem cells. These investigators are planning to go to human trials with this very exciting and promising new drug. They have also developed another peptide drug, PNC-2, that when linked to penetratin (an amino acid) causes malignant cells to revert to normal. It blocks the tumor effect while leaving the normal counterpart protein intact.

Brooklyn VA Medical Center

Kanovsky M, Michl J, Botozlaki G, Morin J Kovac C, Chung D, Chie L, Friedman FK, Pincus MR. Peptides Designed from Molecular Modeling Studies of the ras-p21 Protein Induce Phenotypic Reversion of a Pancreatic Carcinoma Cell Line But Have No Effect On Normal Pancreatic Acinar Cell Growth. *Cancer Chemother Pharmacol.* 2003, 52, 202-8.

9. BACTERIA LINKED TO COMPLICATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Patients with COPD often have exacerbations of the disease that are marked by wheezing and difficult breathing, increased coughing, and increased sputum production. The cause of these exacerbations has been unclear, and whether or not infection is involved has been debated for decades. Now, a team of VA pulmonologists has reported that bacterial infections may indeed cause acute exacerbations of COPD. Using state of the art molecular typing of bacteria found in sputum of COPD patients, the researchers found that new strains of bacteria were much more likely to be found during exacerbations. This offers strong

support for the causative role of bacterial infection in exacerbations of COPD and points the way for rational therapy.

Buffalo VA Medical Center

Sethi S, Evans N, Grant BJ, Murphy TF. New strains of bacteria and exacerbations of chronic obstructive pulmonary disease. New Engl J Med 347:465-71, 2002.

10. ORAL DRUG HAS POTENTIAL TO TREAT SMALLPOX

Researchers at the VA San Diego Healthcare System, in collaboration with scientists at US Army Medical Research Institute for Infectious Disease, Fort Detrick, Maryland, and the University of Alabama, Birmingham, have developed an oral drug that halts the deadly action of smallpox and related pox viruses in laboratory tissue culture cells and in pox-infected mice. The drug, hexadecyloxypropyl-cidofovir (HDP-CDV), blocks the activity of a variety of smallpox virus strains by halting their ability to replicate and spread. It must undergo additional testing in animals and safety trials before being approved for use in humans. However, in view of the threat of bioterrorism using the smallpox virus, and the absence of any effective treatment, the potential for developing HDP-CDV as an oral drug smallpox treatment in humans is timely and highly significant.

San Diego VA Medical Center

Kern EA, Hartline C, Harden E, Keith K, Rodriguez N, Beadle JR, Hostetler KY. Enhanced Inhibition of Orthopoxvirus Replication In Vitro by Alkoxyalkyl Esters of Cidofovir and Cyclic Cidofovir. Antimicrobial Agents and Chemotherapy 2002; 46(4):991-5.

11. ALTERED GENE ACTIVITY IN SCHIZOPHRENIA

VA researchers have compared gene activity in postmortem brain tissues obtained from schizophrenic and normal patients. They detected different levels of activity of myelination-related genes, active in cells called oligodendrocytes, and hypothesize that these cells may be functionally deficient in

schizophrenia. Myelination is the development of an insulating layer around nerve fibers, and myelinated nerves conduct impulses more rapidly than nonmyelinated nerves. The variations in gene activity identified in this study have relevance for several biological processes, notably in the transmission of impulses between nerve cells. This work will lead to further study of the causes of schizophrenia using gene expression analysis.

Bronx VA Medical Center

Hakak Y, Walker JR, Li C, Wong WH, Davis KL, Buxbaum JD, Haroutunian V, and Fienberg AA. Genome-wide expression analysis reveals dysregulation of myelination-related genes in chronic schizophrenia. Proceedings of the National Academy of Science USA 2001, 98(8):4746-51.

12. IMPROVING SURVIVAL AMONG AIDS PATIENTS

In people with human immunodeficiency virus (HIV), co-infection with the hepatitis G virus (known as GBV-C) is associated with slower progression to acquired immunodeficiency syndrome (AIDS). GBV-C is related to hepatitis C virus but does not appear to cause liver disease. GBV-C and HIV have similar modes of transmission via sexual contact and exposure to infected blood or blood products, and HIV-infected patients exhibit an increased prevalence of GBV-C infection. VA researchers have recently shown that mortality associated with HIV infection is significantly lower, over a four-year period, in patients co-infected with GBV-C. Furthermore, the replication of HIV was inhibited in blood cells doubly-infected with GBV-C. These observations represent a major step forward in understanding the natural history of HIV infection and the pathogenesis of AIDS. Although the molecular mechanisms underlying GBV-C inhibition of HIV replication are unknown, it is very probable that this phenomenon contributes significantly to the delayed progression to AIDS and enhanced survival. The GBV-C virus may open a novel therapeutic window for the future treatment or

control of HIV and AIDS.

Iowa VA Medical Center

Xiang J, Wunschmann S, Diekema DJ, Klinzman D, Patrick KD, George SL, Stapleton JT. Effect of coinfection with GB virus C on survival among patients with HIV infection. New England Journal of Medicine, 2001 Sept, 345 (10):761-2.

Clinical Science Research and Development



Large-scale definitive clinical research on health issues are vital to our nation's veterans. These national research studies are organized in the Clinical Science R&D service (CSR&D) by health care categories particularly prevalent in the veteran population that we serve, including age-related changes, special populations (e.g., women veterans, Gulf war veterans, homeless veterans, etc.), health systems (e.g., health care delivery, organization, quality and outcomes), chronic diseases, mental illness, substance abuse and addictive disorders, sensory disorders and loss, acute and traumatic injury, and military and environmental exposures, to name a few.

Results from our studies, a few of which are mentioned here, not only inform our patients and providers about the best treatment choices, but also inform our policy makers and managers about the costs and consequences of new and existing treatments. CSR&D's strengths lie in its ability to organize multiple medical centers to conduct more definitive research than what may be achieved in single-site studies. We strive to address pressing health care concerns and issues that will ultimately allow us to provide the best possible care for those who have served our country.

Brian G. Schuster, MD, FACP
Director

1. SELF-TESTING MAY IMPROVE CARE FOR PATIENTS AT RISK FOR STROKE

Patients at risk for stroke and receiving anticoagulation therapy usually visit a doctor's office once or twice a week for testing to ensure their blood is thin enough to prevent clotting but not so thin as to cause excessive bleeding or hemorrhage. VA researchers will follow about 3,200 patients at 32 VA Medical Centers for three years in one of the few studies to directly compare patient self-testing (PST) to other approaches of anticoagulation management. They expect to demonstrate that PST will decrease the number of strokes, bleeding and related deaths and to improve anticoagulation. PST may also permit more intense monitoring and increased patient participation in the care as safety, quality and convenience are increased.

CSP Study #481

2. A PROMISING THERAPY FOR HUMAN AUTOIMMUNE DISEASES

Inflammatory Thymic 1 (Th1) cells reacting to tissue/myelin-derived proteins called antigens are thought to contribute significantly to the pathogenesis of autoimmune diseases such as multiple sclerosis (MS), rheumatoid arthritis (RA) and psoriasis. A number of T cell receptor (TCR) peptides present on pathogenic Th1 cells have been identified. Dr. Vandembark and his team at the Portland VA Medical Center have used several of these peptides as vaccines. TCR peptide vaccines were used to treat a total of 171 MS patients, 484 RA patients, and 177 psoriasis patients. Their results demonstrated that TCR peptide vaccination is safe and well tolerated, and can produce significant clinical improvements in a subset of patients that respond to immunization. This study represents a promising approach for treating complex autoimmune diseases.

Portland VA Medical Center

Vandembark AA, Morgan E, Bartholomew R, Bourdette D, Whitman R, Carlo D, Gold D, Hashim G, Offner H. TCR peptide therapy in human autoimmune diseases. Neurochem Res. 26(6):713-30, 2001.

3. TAKING THE LEAD IN CORONARY ARTERY BYPASS SURGERY

VA has been a leader in defining the effectiveness of leg vein and internal mammary grafts as conduits for coronary artery bypass surgery throughout the years. Since the 1970s, new techniques have emerged to look at alternative methods of harvesting vessels, specifically from the radial (arm) area instead of the leg area. These procedures were soon abandoned, however, as these veins tended to produce spasms and the procedure was technically very difficult. This study will now introduce calcium channel blockers to prevent vascular spasms in patients with coronary artery disease and may lead to a higher graft success rate after surgery.

CSP Study #474

4. HOMOCYSTEINE AND CORONARY HEART DISEASE

For more than 20 years, many epidemiological studies have shown that an elevated plasma level of the amino acid homocysteine was significantly and independently associated with an increased risk of coronary heart disease and death. High homocysteine levels can produce blood clots more easily and results in increased risk of blood vessel blockages leading to a stroke or other blood flow problems. Researchers at the Boston VA Medical Center will test whether folate, pyridoxine, and vitamin B12 can lower levels of homocysteine and coronary heart disease rates. It will be conducted with patients who already have elevated homocysteine levels, such as those with chronic renal failure and end-stage renal disease. By screening for patients with high plasma homocysteine concentrations and measuring the levels after three months, the study may determine if the hypothesized reduction in death and cardiovascular event rates are associated with a decrease in plasma homocysteine concentration.

CSP Study #453

5. UNDERSTANDING THE GENETIC ROLE IN TREATING DISEASE

The mapping and sequencing of the human genome promises rapid growth in understanding the genetically-influenced mechanisms that underlie human disease. Genetic tissue banking provides opportunities to analyze the genetic role in response to treatments. This study will address one approach to the solution of the concerns about subjects' rights, informed consent, privacy, and ownership of genetic material. It will include a central repository for DNA and other genetic tissue specimens, a scientific advisory committee, an ethical oversight committee, a veterans' advisory group, and a coordinating center to administer the tissue bank.

CSP Study #478

Lavori PW, Krause-Steinrauf H, Brophy M, Buxbaum J, Cockroft J, Cox DR, et. al. Principles, organization, and operation of DNA bank for clinical trials: a Department of Veterans Affairs cooperative study. Controlled Clinical Trials, 2002 Jun;23(3);222-39.

6. PREVENTING THE PAIN OF SHINGLES

The painful rash associated with shingles can interfere with a patient's ability to perform essential activities of daily living, resulting in a loss of independence that is emotionally devastating and frequently irreversible. The most common complication of shingles is post-herpetic neuralgia, severe pain that may persist long after the shingles rash heals. It frequently results in disordered sleep, chronic fatigue, anxiety and severe depression. Antiviral therapy has a modest impact on the acute phase of shingles, but it does not appear to prevent the development of post-herpetic neuralgia. This five-year study may determine whether vaccinations with varicella-zoster decreases the incidence and/or severity of shingles. More than 37,000 subjects over 60 years of age will receive either the vaccine or the placebo at 22 medical centers nationwide.

CSP Study # 403

7. GROUP TREATMENT MODEL FOR PTSD

No proven, effective treatment has been found for the devastating effects of post-traumatic stress disorder (PTSD). One recent study found that trauma focus group therapy did not have a significant impact on PTSD treatment. A new study will assess the effectiveness of prolonged exposure (PE) vs. present-centered therapy (PCT) for treatment of PTSD due to military-related trauma in women veterans. PE will consist of 10 weekly treatment sessions that include education about and exposure to the memories of the trauma; PCT will consist of a control therapy of the same duration to provide emotional support for the trauma victim.

CSP Studies #420 & #494

8. MILLENNIUM COHORT STUDY

This ongoing study will compare the changes in health status between deployed and non-deployed personnel over a 21-year period in order to determine the health impact of deployments and other aspects of military service. It will examine 100,000 military personnel, including a cross-sectional sample of those deployed to Southwest Asia, Bosnia, or Kosovo since August 1997. Approximately 30,000 participants have enrolled since November 2001. The actual change in health and functional status of the participants will be tracked through repeated questionnaires by postal and internet access. In addition, information on morbidity and mortality will be captured using VA and non-VA medical care, hospitalization, and death file databases. It is a collaborative study with the Department of Defense.

CSP Study #505

9. REDUCING THE EFFICACY-EFFECTIVENESS GAP IN BIPOLAR DISORDER

Bipolar disorder is a mental illness characterized by the presence of at least one episode of elevated or irritable moods lasting at

least one week. A major depressive episode is very common in the lifetime of individuals with bipolar disorder. This population continues to rise within the VA, from 5.8% in FY99 to 9.4% in FY00. In FY01 alone, VA treated over 65,000 veterans with bipolar disorder. In addition to the chronicity, medication side effects and diminished function, numerous studies indicate that patients with mental illness have a greater risk of premature death than the general population. Caring for this vulnerable population represents a major and costly responsibility for VA. Standard treatment to prevent or lessen the severity of episodes of depression or mania include psychotherapy and/or medications. This study will examine the effects of a high-intensity ambulatory treatment program for bipolar disorder compared to standard office-based, physician-centered care. It will compare the disease-specific outcomes and the functional outcomes to overall treatment costs.

CSP Study #430

10. TREATING ALCOHOL DEPENDENCE WITH NALTREXONE

Although the drug naltrexone has been approved by the Food and Drug Administration for the treatment of alcohol dependence, its effectiveness is uncertain. Naltrexone blocks the opioid receptors in the brain and should therefore block the euphoric effect and craving for alcohol. This can in turn block the vicious cycle of alcohol addiction in which one drink nearly always leads to a full-blown relapse. Researchers at the West Haven VA Medical Center have completed a study with 627 patients that compared naltrexone as an adjunct to the standardized psychosocial treatment. After 52 weeks of treatment, there were no significant differences among the various study groups in the percentage of days on which drinking occurred and the number of drinks per drinking day. VA researchers therefore did not support the use of naltrexone for the treatment of men with chronic and severe alcohol

dependence.

West Haven VA Medical Center

Krystal JH, Cramer JA, Krol WF, Kirk GF, Rosenheck RA. Naltrexone In the treatment of alcohol dependence. New England Journal of Medicine, 2001 Dec, 345(24):1770-1.

11. PREVENTION OF PROSTATE CANCER

VA is participating in a National Cancer Institute-sponsored study that is the first clinical trial designed to determine if dietary supplements (Vitamin E and selenium) prevent prostate cancer. This is the most common cancer in the VA healthcare system and measures to prevent it would be of great impact to the VA and the nation's veterans. It is the second most common cancer in the United States and is the leading cause of cancer death among elderly U.S. men. Approximately 209,900 men in the United States are diagnosed with prostate cancer every year and nearly 42,000 die annually. VA will provide nearly 40 medical sites and 6,000 patients for the 12-year Selenium Vitamin E Cancer Prevention Trial (SELECT) that began in July 2001. The study is intended to produce a new understanding and insight of the disease.

CSP Study #499

12. PREVALENCE OF HEPATITIS C INFECTION IN VETERANS

Hepatitis C is a common infection with a variable course that can lead to chronic hepatitis, cirrhosis, and liver cancer, and is the leading reason for liver transplantation in the United States. The course of illness may be adversely affected by various factors, especially alcohol consumption. According to the National Health and Nutrition Examination Survey of 1988-94 and other population-based surveys, nearly 4 million Americans are infected with hepatitis C. Approximately 30,000 acute new infections occur each year, about 25-30 percent of which are diagnosed and responsible for an estimated 8,000-10,000 deaths annually.

Without effective intervention that number may triple in the next 10-20 years. VA researchers are conducting a study to determine the prevalence of hepatitis C virus infection in veterans that are treated at VA Medical Centers. The study will include 4,000 veterans at 20 VA Medical Centers.

CSP Study #488

Health Services Research and Development



The Health Services Research & Development service (HSR&D) focuses on identifying cost-effective strategies for organizing and delivering healthcare and optimizing patient and system-level outcomes. The programs cover a broad span of healthcare research and delivery, including basic research, dissemination of research results, and ultimately applying research results to clinical, managerial, and policy decisions.

Some of the current issues under investigation by HSR&D researchers include telemedicine, pain management, quality improvements in ambulatory and surgical care, outcomes measurement in mental health, cost-effective treatments for patients with substance abuse disorders, and design and implementation of clinical services. A specific area of great interest to veterans in remote areas of VA Medical Centers includes that of telemedicine. While it has the potential to improve both access to care and quality of care, many questions remain about the effectiveness of telemedicine applications. VA is expanding efforts to determine what works and why, and how we can best use telemedicine to improve the quality of care for veterans.

HSR&D is at the center of a unique opportunity—and a vital part—of searching for solutions to today’s healthcare challenges, including VA’s mission to embrace new and integrated models of healthcare, and to improve service, quality, and overall efficiency. A few of our recent findings are stated below.

Shirley Meehan, MBA, PhD
Acting Director

1. BETTER PROVIDER COORDINATION REDUCES DIABETES-RELATED AMPUTATIONS

Patients with diabetes and foot ulcers are at increased risk for hospitalization, infection, and amputation. Studies have reported that well-coordinated, sustained foot care can reduce diabetes-related complications by 50%. Researchers sought to determine if healthcare organizations with well-defined organizational functions and roles, higher levels of communication, and formal and informal feedback would provide better foot care with fewer amputations. Participants in the study included all providers involved in diabetes-related foot care and a random sample of primary care providers from 10 VA Medical Centers representing different geographic regions. The study was conducted in two phases. Phase 1 consisted of a mailed provider survey and site visits in which providers involved with diabetes-related foot care (e.g., vascular and orthopedic surgeons, podiatrists, wound care specialists) and primary care providers were interviewed, and amputation rates were assessed. Phase 2 consisted of a mailed patient survey, medical record abstraction, and foot care cost analysis. Results showed that patients with higher levels of programming coordination and feedback coordination had significantly lower amputation rates. Researchers suggest that in order to minimize patients' diabetes-related amputation rates, programming coordination should be emphasized (i.e., coordinated use of electronic medical records, policies, procedures, protocols, internal education, and training).

Wrobel JS, Charns MP, Diehr P, Robbins JM, Reiber GE, Bonacker KM, Haas LB, Pogach L. The relationship between provider coordination and diabetes-related foot outcomes. *Diabetes Care* 2003 Nov;26(11):3042-7. DIS 99-037

2. INNOVATIVE STRATEGIES IMPROVE CHRONIC HEART FAILURE CARE

Recently, clinical practice guidelines to treat chronic heart failure (CHF) were revised to incorporate the widespread use of beta-blockers. This study focused on finding the most effective strategy to implement this therapy in veterans with CHF. In phase 1 of the study, researchers tried three approaches: 1) the usual approach—intensive provider education and guideline promotion (control group); 2) a “Provider notification/Patient empowerment” strategy using computerized reminders and informational letters, respectively; and, 3) a specially-trained nurse facilitator who, with approval from the patients' physicians, contacted potential beta-blocker candidates and then assumed responsibility for initiation and up-titration of beta-blocker therapy. Results indicate that the nurse facilitator initiated or up-titrated 67% of those patients assigned to her, compared with 16% in the provider notification group and 27% in the control group. In addition, the mean length of time from initiation of beta-blockers to achieving the target dose was shortest among those treated by the nurse facilitator: 5.9 months compared to 9.3 months (provider notification) and 8.5 months (control). Since beta-blockers have been consistently found to reduce mortality by 35% and hospitalizations by 25-40% for patients with a heart failure diagnosis, this nurse facilitator intervention could have a great impact on the outcomes and costs of heart failure management.

Ansari MN, Shlipak, MG, Heidenreich PA, Massie BM. Strategies to improve guideline adherence: a randomized clinical trial. *Journal of the American College of Cardiology* 2002 Mar; 39 (5 Suppl A [American College of Cardiology 51st Annual Scientific Session abstracts]).

Massie BM. Treating heart failure: it's time for new paradigms and novel approaches. *Journal of Cardiac Failure* 2002 Jun;8(3):117-119. CHI 99-063

3. HIV THERAPY DOES NOT INCREASE RISK OF VASCULAR DISEASE

A study evaluating the relationship between HIV treatment and cardiovascular and cerebrovascular disease found that large increases of antiretroviral therapy by HIV-infected VA patients in the second half of the 1990s were accompanied by small decreases in cardiovascular and cerebrovascular events, and large decreases in death rates. Contrary to previous reports, these findings suggest that fear of accelerated vascular disease should not deter patients and providers from employing the highest quality HIV care, as defined by the use of guideline-recommended combination antiretroviral therapy.

Bozzette SA, Ake CF, Tam HK, Chang SW, Louis TA. Cardiovascular and cerebrovascular events in patients treated for human immunodeficiency virus infection. The New England Journal of Medicine 2003 Feb 20;348(8):702-10. QUERI HIV

4. BLOOD PRESSURE CONTROL MOST IMPORTANT MEDICAL INTERVENTION FOR TYPE 2 DIABETES

The majority of adverse diabetes outcomes are a result of vascular complications, such as coronary artery disease. A highly prevalent risk factor for these complications is hypertension, which is extremely common among persons with type 2 diabetes. Researchers conducted a literature review to determine optimal blood pressure (BP) goals and the most effective medications for the treatment of hypertension in type 2 diabetes. The review was limited to randomized controlled trials that included patients with diabetes in which major clinical endpoints (all-cause mortality, cardiovascular mortality and major cardiovascular events) were included. These trials evaluated either an antihypertensive drug versus placebo, or compared the effects of different target blood pressure levels on diabetes outcomes. In addition, trials included in the literature review examined the effects of different classes of

drugs; for example, angiotensin-converting enzyme (ACE) inhibitors compared with calcium channel blockers. Results show that improved blood pressure control in patients with type 2 diabetes leads to substantially reduced risks of cardiovascular events and mortality. Researchers recommend, however, that hypertension be prioritized and stressed as the most important intervention for this patient population. Further, results showed that ACE inhibitors and angiotensin-II receptor blockers appear to be the best first-line treatments for control of hypertension.

Vijan S, Hayward RA. Treatment of hypertension in type 2 diabetes mellitus: blood pressure goals, choice of agents, and setting priorities in diabetes care. Annals of Internal Medicine 2003 Apr 1;138(7):593-602. RCD

5. VA PATIENTS SHOW GREATER ADHERENCE TO STATIN THERAPY

Several studies analyzing lipid management among patients with coronary heart disease (CHD) show that lipid-lowering drugs, particularly statins, are an effective therapy in the secondary prevention of CHD. It is estimated that compliant statin therapy can prevent 12.4 serious cardiovascular events per 1,000 patients, per year. Researchers set out to determine: 1) the persistence of statin use in patients with CHD; 2) the difference in persistence between established and new users; and, 3) the characteristics associated with poor persistence. The study included nearly 9,000 male VA patients with CHD who were prescribed statins from July 1999 through June 2000, and were then followed for 18 months. For VA patients, investigators found a compliance rate of 71% after 18 months—a relatively high compliance rate when compared to a U.S. study showing only 40% after 12 months. VA patients' higher compliance rate may be due to a number of reasons, such as low drug co-payments and a longer supply of refills. The VA system also routinely encourages statin use by promoting clinical guidelines and computer reminders.

Kopjar B, Sales AE, Pineros SL, Sun H, Li YF, Hedeem AN. Adherence with statin therapy in secondary prevention of coronary heart disease in Veterans Administration male population. *American Journal of Cardiology* 2003 Nov 1;92(9):1106-8. QUERI IHD

6. LOWER SCREENING RATES FOR COLORECTAL VERSUS PROSTATE CANCER

While some believe prostate-specific antigen (PSA) screening may reduce prostate cancer deaths, others believe that widespread screening will lead to more prostate cancer diagnoses and potentially harmful therapy, without any improvement in outcomes. No evidence yet exists to support either theory. On the other hand, colorectal cancer screening for people 50 and older is widely advocated, and has proven to substantially reduce mortality among those who receive periodic screening. Researchers compared the prevalence of PSA and colorectal cancer screening among men in the United States. Using data from a large telephone survey conducted by the Centers for Disease Control and Prevention (n = 49,315), they found that 75% of men aged 50 and older had undergone PSA testing at least once, compared to 63% of men aged 50 and older who had undergone colorectal cancer screening. Further, men were more likely to be up to date on prostate screening than colorectal cancer screening. This suggests that despite widespread efforts to improve adherence to colorectal cancer screening guidelines, it is still considerably less common than prostate cancer screening. Researchers recommend that physicians inform patients about the known mortality benefit of colorectal cancer screening, as well as the uncertainty about screening for prostate cancer.

Sirovich BE, Schwartz LM, Woloshin S. Screening men for prostate and colorectal cancer in the United States: does practice reflect the evidence? *Journal of the American Medical Association* 2003 Mar 19;289(11):1414-20. RCD 97-312

7. COMMUNITY-BASED CARE MEASURES UP

More than 240 Community-Based Outpatient Clinics (CBOCs) have been established across the country, with the goals of increasing access to care, shortening waiting times for visits, and increasing quality while decreasing the cost of care. A team of HSR&D investigators was charged with evaluating key aspects of CBOCs and then comparing the services CBOCs provide with the same services provided at VA Medical Centers. Researchers found that (1) Patients in CBOCs perceive fewer problems with access and timeliness of care (e.g., shorter waiting times) than do traditional VA clinic patients; (2) CBOCs provide a similar level of quality of care as VA Medical Centers in regard to prevention and disease detection; (3) Total costs of care for veteran patients at CBOCs are lower compared to costs of care for patients treated VA Medical Centers. Findings suggest that CBOCs have the potential to enhance access to primary care for veterans, without sacrificing quality.

Series of CBOC articles appeared in Medical Care 2002 Jul;40(7):555-95. MRR 98-015

8. VA DECREASES HOSPITAL LENGTH OF STAY

Since a major health care reorganization in the mid-1990s, VA has reduced inpatient beds and inpatient admissions by nearly 52% and 32%, respectively, and has opened more than 200 community-based primary care clinics. However, little data exists on differences between VA and other U.S. hospitals regarding inpatient utilization. This retrospective cohort study compared length of stay (LOS) in VA hospitals to a representative sample of private sector and non-federal government hospitals, using random samples from publicly available administrative data for patients discharged between 1996 and 1999. During the study period, differences in LOS between VA and non-VA hospitals decreased substantially, from

2.9 days in 1996 to 1.6 days in 1999.

Rosenthal GE, Kaboli PJ, Barnett MJ. Differences in length of stay in Veterans Health Administration and other United States hospitals: is the gap closing? Medical Care 2003 Aug;41(8):882-94. VCR 99-013

9. PTSD DISABILITY BENEFITS FAVOR COMBAT-EXPOSED VETERANS

Post-traumatic stress disorder (PTSD) is the most common psychiatric condition for which veterans seek VA disability benefits. Veterans with compensative medical or psychiatric conditions related to or aggravated by their military service, such as PTSD, are said to be “service-connected” and receive priority care at VA medical facilities. Studies indicate that women have a higher prevalence of PTSD than men, however, women veterans are less likely than men to receive disability awards on the basis of PTSD. This study sought to determine whether there are gender discrepancies in rates of service connection for PTSD, and, if so, whether or not they could be attributed to the severity of illness or impairment. Investigators surveyed more than 3,000 veterans (male and female) seeking VA disability benefits for PTSD, and then conducted claim audits on 11% of the sample. Factors taken into consideration during analysis included: current PTSD symptom severity, combat exposure, in-service sexual trauma, and level of functional impairment. Results showed no gender bias. Instead, researchers found evidence of a combat advantage. More than 90% of combat-injured veterans, regardless of gender, became service-connected for PTSD. This advantage was not limited only to combat-injured veterans but extended to veterans with combat exposure in general.

Murdoch M, Hodges J, Hunt C, Cowper D, Kressin N, O'Brien N. Gender differences in service connection for PTSD. Medical Care 2003 Aug;41(8):950-61. GEN 97-002

10. FLU AND PNEUMONIA VACCINES IMPROVE PREVENTIVE CARE FOR SCI PATIENTS

Vaccination is especially important for individuals with spinal cord injury and disease (SCI&D), who are more likely to die if they contract influenza or pneumonia than those in the general population. The SCI Quality Enhancement Research Initiative (QUERI), working with 23 VHA SCI centers across the country, implemented four interventions to increase vaccination rates for individuals with SCI&D. The interventions were successful, and both influenza and pneumonia vaccination rates increased across all 23 SCI centers.

Legro M. Maximizing vaccination rates for veterans with SCI&D. VA Office of Research and Development, HSR&D. QUERI Quarterly 2002 Mar;3(4):2. QUERI SCI

11. UNDERSTANDING PATIENTS' END-OF-LIFE TREATMENT PREFERENCES

There is considerable debate whether end-of-life care is delivered according to what patients and their families desire. This study examined information for terminally ill older patients, their families, and their physicians, regarding discussions about prognosis, treatment choices, and how these treatment choices are made. Using a newly-developed instrument—the WALT (Willingness to Accept Life-Sustaining Treatment), researchers found that when participants had the option of low-burden treatment with an expected return to good health, 98.7 percent chose to receive that treatment. However, only 11.2 percent chose an option where surviving a high-burden treatment would result in severe functional or cognitive impairments, thereby proving that treatment burden and outcome expectancies greatly influence treatment preferences.

Fried TR, Bradley EH, Towle VR, Allore H. Understanding the treatment preferences of seriously ill patients. New England Journal of Medicine 2002 Apr 4;346(14):1061-6.

12. PHARMACY DATA PREDICTS ADMISSION RATES FOR PATIENTS WITH SCHIZOPHRENIA

Researchers recently found that among patients with schizophrenia, antipsychotic medication adherence was strongly associated with rates of psychiatric hospital admission. For more than 2 million Americans with schizophrenia (about 100,000 of whom are veterans), antipsychotic medications can significantly reduce symptoms and are an essential part of treating the disorder. However, many patients do not adhere to their prescribed medication regimen. Using pharmacy data, researchers examined the relationship between outpatient adherence to antipsychotic medications and hospital admissions. Findings show that patients with poor medication adherence were more than twice as likely to be admitted as patients with good adherence and spent more days in the hospital. This study indicates that healthcare systems may be able to use pharmacy data to identify poorly adherent patients who are at increased risk for hospitalization and would benefit from intervention.

Valenstein M, Copeland LA, Blow FC, McCarthy JF, Zeber JE, Gillon L, Bingham CR, Stavenger T. Pharmacy data identify poorly adherent patients with schizophrenia at increased risk for admission. Medical Care 2002 Aug;40(8):630-9.

Rehabilitation Research and Development



The Rehabilitation Research and Development (RR&D) service strives to advance the state-of-the-art rehabilitative healthcare for veterans. Special RR&D centers located at VA facilities nationwide attract the best and brightest minds from clinical practice that foster productive relationships with academia and industry. These centers focus on the rehabilitative theme of functional loss and restoration, as associated with physical impairments, as well as diseases and disorders. Specifically, center research endeavors encompass a myriad of clinical and basic research, such as improving mobility in veterans with neurological or orthopaedic impairments via the utilization of functional electrical stimulation, or the lower-limb prosthetics to early detection of hearing and vision loss.

Progress by clinician researchers makes it possible to anticipate great strides in functional recovery that in turn increases independence for patients. An increasing arsenal of rehabilitative therapies that focus not only on adaptation but restoration is now a reasonable expectation. The next few decades hold tremendous promise for clinical advances in rehabilitative care for veterans who suffer from disability or impairment. We are very proud of all the RR&D researchers and are excited about the promise shown in all our funded studies. The following summaries are just a few of our achievements in the last two years.

Mindy Aisen, MD
Director

1. PHARMACEUTICAL AGENTS MAY IMPROVE MEDICAL COMPLICATIONS OF SPINAL CORD INJURY

The secondary complications that are associated with chronic spinal cord injury (SCI) often interfere to a greater extent with the personal and professional functions of veterans than does the actual paralysis. Complications often stifle independence and reintegration into society. To this end, researchers at the newly established Bronx VA RR&D Center have undertaken a coordinated research effort to study and develop novel therapies to the medical consequences of SCI. Physicians and scientists are dedicated to ascertaining the mechanisms that underlie the medical complications of persons with SCI. Preliminary results of an array of their studies reveal that a long-acting β 2-adrenergic agonist has the ability to increase the strength of breathing; neostigmine is effective in improving bowel motility; testosterone replacement therapy improves body composition as well as associated adverse metabolic and autonomic changes; anabolic steroid therapy returns physical function to baseline status after inter-current illness; and, a gamma-aminobutyric acid agonist increases growth hormone insulin-like growth factor-1 levels to “youthful” values. Such results are potentially medical significant in that anabolic agents may someday be considered in the routine care of persons with chronic SCI to reduce some of the respiratory, gastrointestinal, cardiovascular-autonomic, and endocrine-metabolic complications. Such research results can in turn improve the quality of life of veterans with SCI and reduce associated morbidity.

Bronx VA Medical Center

RR&D Project Number: B2701C

2. IMPROVING SPEECH IN SCI PATIENTS AFTER INTENSE THERAPY

Constraint Induced Language Therapy (CILT) has been modeled after the successful Constraint Induced Movement Therapy, which uses intensive and focused motor therapy to

restore limb strength in patients after stroke. A pilot project, resulting from collaboration between the Houston and Gainesville VA RR&D Centers, is based on the hypothesis that similar intensive therapies for aphasia will result in improvement in language function. Although results are preliminary, chronic aphasic (characterized by a duration longer than 4 years and severely non-fluent) patients have shown the ability to speak in phrases after intensive therapy. Researchers are hopeful that a rigorous study will lead to effective treatments and a better understanding of cognitive rehabilitation.

*Gainesville and Houston VA Medical Centers
RR&D Project Number: C2670C*

3. WHEELCHAIR USE MAY EXPOSE PEOPLE WITH DISABILITIES TO HARMFUL VIBRATIONS

Little is known about how dynamic acceleration impacts wheelchair rider comfort. Researchers at the Pittsburgh RR&D Center conducted a study to test the operation of an instrumented wheelchair over a Simulated Road Course (SRC) and the operation of the instrumented wheelchair during the users’ normal daily activities. Results of this study indicate that wheelchair vibrations may contribute to fatigue among manual wheelchair users and could lead to injury. Furthermore, there is some evidence that suspension casters may reduce vibration exposure; however current status of rear suspension designs may not be able to reduce shock or vibration exposure. Suspension caster forks reduce the shock and vibration exposure to the user of a manual wheelchair. Rear suspension systems reduce some of the factors related to shock and vibration exposure, but they are not clearly superior to traditional designs.

Pittsburgh VA Medical Center

RR&D Project #: B805-RC

*VanSickle DP, Cooper RA, Boninger ML, DiGiovine CP.
Analysis of Vibrations Induced during Wheelchair
Propulsion. Journal of Rehabilitation Research &*

4. POWER-ASSISTED MANUAL WHEELCHAIR REDUCES STRESS

Pushrim-activated, power-assisted wheelchairs (PAPAWs) have been found to reduce the energy demand placed on the user during propulsion. This concept has been rated favorably among wheelchair users who do not want to compromise their current activities by using standard manual or powered wheelchairs. Study results indicate that users found the PAPAW a less physiologically stressful means of mobility with few adaptations to their vehicle or home environment.

Cooper RA, Corfman TA, Fitzgerald SG, Boninger ML, Spaeth DM, Ammer W, Arva J. Performance Assessment of a Pushrim Activated Power Assisted Wheelchair. IEEE Transactions of Control Systems Technology 2002; 10:121-6.

Cooper RA, Fitzgerald SG, Boninger ML, Prins K, Rentschler AJ, Arva J, O'Connor TJ. Evaluation of a Pushrim-Activated Power Assisted Wheelchair. Archives of Physical Medicine and Rehabilitation 2001; 82:702-8.

5. ADVANCES IN TECHNIQUES AND INSTRUMENTATION FOR THE EARLY DETECTION OF OTOTOXICITY

Individuals who receive therapeutic drugs having “ototoxic” potential for the treatment of various medical conditions may incur ototoxic hearing loss as a treatment side effect, particularly the aminoglycoside antibiotics and the chemotherapeutic agent cisplatin. It is possible to minimize or avert ototoxicity altogether, but it must be detected early enough to preserve post-treatment quality of life. Researchers at the National Center for Rehabilitative Auditory Research (NCRAR) have conducted research for early detection of ototoxicity resulting in national guidelines for ototoxicity monitoring. The guidelines are endorsed and published by the American Speech-Language-Hearing Association and are used at many healthcare facilities in their

ototoxicity-prevention programs. More recent efforts at the NCRAR have focused on developing new techniques for detecting ototoxicity that do not rely on a patient’s active response. These objective techniques include the measurement of distortion product otoacoustic emissions (DPOAE) and auditory brainstem responses (ABR). DPOAEs measure the function of hair cells in the inner ear, which are thought to be most susceptible to early ototoxic effects. Earliest identification of ototoxicity may require detection of hair cell damage in the high frequencies. High-frequency DPOAE methods have been developed using instrumentation that was specially engineered for this purpose. High-frequency ABR methods have also been developed, and have been shown to be effective for early detection of ototoxicity. Research at NCRAR is leading to further standardization of methods for early detection of ototoxicity, which is necessary to make ototoxicity monitoring a standard level of healthcare for veterans and those nationwide who receive therapy with ototoxic drugs. *Portland VA Medical Center*

Fausti SA, Campbell K, Helt W, Gordon J. Ototoxicity monitoring: key elements and procedures. 13th Annual Convention & Exposition, American Academy of Audiology, San Diego, CA, April 19-22, 2001.

6. NEW TECHNIQUES FOR MEASURING TINNITUS

Tinnitus is a subjective symptom where worldwide efforts to quantify its acoustical aspects have not yet produced a widely accepted method for treatment. Researchers in Portland, however, have developed automated computer methods to measure tinnitus loudness and pitch that are not only reliable but are capable of standardization. The focus of the study is to standardize methods of evaluation and treatment of tinnitus as VA provides \$172.7 million per year for disability compensation to more than 162,000 veterans.

Henry JA, Schechter MA, Nagler SM, Fausti SA.

Comparison of tinnitus masking and tinnitus retraining therapy. *Journal of the American Academy of Audiology* 2002 Nov-Dec;13(10):559-81.

Henry JA, Flick CL, Gilbert AM, Ellingson RM, Fausti SA. Comparison of two computer-automated procedures for tinnitus pitch-matching. *Journal of Rehabilitation Research & Development* 2001; 38:557-66.

7. THERAPEUTIC EFFECTS OF EXERCISE AFTER STROKE

More than a half million people in the U.S. suffer strokes each year. The majority survive because of advances in treatment, however, nearly 40 % result in physical disabilities, including hemiparesis, or weakness on one side of the body. This study will examine the effects of resistance exercise on the recovery of muscle function that has been impaired and damaged by stroke. Results will form a basis for prescription of appropriate, timely, and effective clinical interventions.

RR&D Study #B2792R

8. OSSEOINTEGRATED PROSTHESES

Osseointegration – the direct attachment of titanium to bone of residual limbs that allows direct attachment of functional prostheses – offer patients improved sensory feedback and psychological acceptance. This technique avoids much of the discomforts and complications associated with traditional prosthetic sockets. VA researchers in San Diego have discovered that implants can become osseointegrated by stimulating natural collagen enzymes without rejection or pain. Osseointegrated prostheses have tremendous potential to supplement current prostheses techniques and are particularly well suited where traditional methods have failed.

Brånemark R, Rydevik B, Myers R. Osseointegration in skeletal reconstruction and rehabilitation: A review. *Journal of Rehabilitation Research & Development* 2001; 38:175-81.

Ysander M, Brånemark R, Olmarker K, Myers R. Intramedullary Osseointegration: Development of a

rodent model and study of histology and neuropeptide changes around titanium implants. *Journal of Rehabilitation Research & Development* 2001; 38:183-90.

9. COMPUTER MODEL MAY HELP PREVENT FOOT AMPUTATIONS

Researchers at the Seattle VA Medical Center have developed a three-dimensional model of the foot and ankle in order to understand, treat, and prevent foot disease that leads to amputation. Musculoskeletal models of the human body are increasingly used to study biological structures; the lower limb in particular as it is the primary physical interaction between the body and the environment during locomotion. The Seattle VA model was generated as an anatomically detailed 3-D reconstruction from 286 computerized topographic (CT) images. In addition to preserving specimens from cadavers for only the most crucial studies, computational models such as this provide data on internal stresses and strains not readily available during cadaveric experiments.

Seattle VA Medical Center

Camacho D, Ledoux W, Rohr E, Sangeorzan B, Ching R. A three dimensional, anatomically detailed foot model: A foundation for a finite element simulation and means of quantifying foot bone position. *Journal of Rehabilitation Research & Development* 2002 May-June;39(3):401-10.

10. DECREASING URINARY TRACT INFECTIONS IN SCI PATIENTS

Management of bowel and bladder care in patients with SCI is expensive, time consuming, and has a dramatic impact on quality of life. Researchers at the Cleveland Functional Electrical Stimulation Center are evaluating the use of electrical control of bowel and bladder function in SCI patients for emptying the bladder and bowel, thus reducing infection and improving continence following spinal cord injury.

Data from a subset of patients in a larger study indicate a substantial decrease in the annual cost

of bladder and bowel care. Preliminary results show that 35 of 38 patients from three VA Medical Centers have been able to use the stimulation system to produce urine on demand with low residual volumes.

Cleveland, Bronx, and San Diego VA Medical Centers

Creasey GH, Dahlberg JE. Economic consequences of an implanted neuroprosthesis for bladder and bowel management. Archives of Physical and Medical Rehabilitation 2001; 82:1520-5.

11. TELE-REHABILITATION FOR VETERANS WITH A LOWER-LIMB AMPUTATION OR ULCER

Timely identification of problems with healing and/or at-home therapy is critical to ensure best care for our veterans. The objective of this study is to design and improve post-discharge care following a recent lower limb amputation or improving leg or foot ulcer treatments using tele-rehabilitation technology. This project will focus on several aspects: (1) comparing the quality of information obtained via tele-rehabilitation versus in-person care; (2) determining the most appropriate tele-rehabilitation method to assess outcome; (3) determining the most effective ways to train patients and providers to use tele-rehabilitation; and (4) discovering ways to encourage patient and provider usage, and finding the limiting factors to patient set-up and usage and more. If tele-rehabilitation shortens the time to healing, reduces complications, and improves adherence to recommended practices, the quality of life for many veterans will be improved. Improved and timely quality of care will then translate into economic savings, as fewer treatments will be necessary.

RR&D Project # A2969R

12. EFFICACY OF FOOTWEAR IN PATIENTS WITH DIABETES

The goal of this study is to determine the efficacy of widespread dispensing of therapeutic shoes and inserts to all diabetic

patients with a history of foot ulcers. Footwear has been implicated as a primary cause of foot ulcers, yet research is limited on the efficacy of shoe and insert combinations to prevent reulceration. A study conducted at the Seattle VA Medical Center addressed whether extra depth and width therapeutic shoes and two types of inserts reduced relocation in diabetic individuals with a history of foot ulcer. The results of this study indicate that special therapeutic shoes confer no significant ulcer reduction compared to control patients' footwear. This trial did not confirm the common assumption that therapeutic shoes and inserts can prevent reulceration in persons without severe foot deformity. Results also suggest that careful attention to foot care by healthcare professionals may be more important than therapeutic footwear. It does not negate the possibility that special footwear is beneficial in persons with diabetes who do not receive such close attention to foot care or in individuals with severe foot deformities.

Reiber GE, Smith DG, Wallace C, Sullivan K, Hayes S, Vath C, Maciejewski M, Yu O, Heagerty PJ. Effect of therapeutic footwear on foot reulceration in patients with diabetes: a randomized clinical trial. Journal of the American Medical Association 2002, 287(19):2552-8.

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