

IMPACTS

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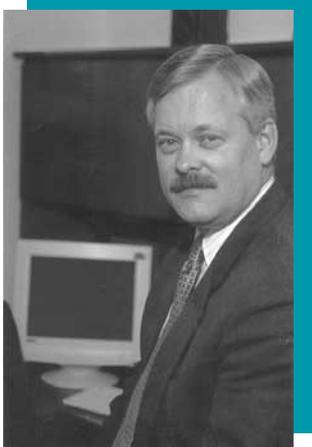
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Impacts 2001

A Message from the Chief Research and Development Officer



The Office of Research and Development (ORD) focuses on health problems prevalent among veterans. This highly accomplished program spans the range of biomedical, clinical, health services, rehabilitation, and epidemiologic research. The mission of the VA research program is to discover knowledge and create innovations that advance the health and care of veterans and the nation. VA scientists are leaders in the development of cutting-edge health-care technology and are dedicated to their commitment in providing the best possible care for our veterans.

While pursuing the common goal of improving health care for veterans and the nation, the four services of VA research each bring unique strengths to our endeavor.

The **Cooperative Studies Program**, that I have the privilege of directing, is one of the most recognized large-scale clinical trial programs in the world. This program determines the effectiveness of new therapies through multi-center clinical trials. Investigators collaborate with colleagues across the nation and around the world to test new treatments that benefit veterans as well as the general population. Ongoing efforts range from testing the effectiveness of a vaccine against shingles in the elderly to determining whether intensified blood-sugar control can prevent major vascular complications in type II diabetes.

The **Medical Research Service** (MRS) is led by Paul Hoffman, M.D., and has a major role in serving veterans through its achievements in basic and clinical research. Major advances and contributions as a result of MRS research include the successful treatment of tuberculosis, the first successful liver transplant, the concept that led to development of CAT scan, drugs for treatment of mental illness, and development of the cardiac pacemaker. New research is focusing on unraveling further the mysteries of cancer, multiple sclerosis, depression, stroke, Alzheimer's disease, Parkinson's disease, and diabetes.

The **Health Services Research and Development Service** (HSR&D) is led by John Demakis, M.D., and is a leader in identifying effective and efficient ways to organize and deliver health care. Eleven HSR&D centers of excellence that focus on linking research to patient care. In addition, the HSR&D Quality Enhancement Research Initiative (QUERI) is translating research results into improved patient care. It targets conditions common among veterans, including chronic heart failure, diabetes, stroke, and spinal cord injury.

The **Rehabilitation Research and Development Service** (RR&D), led by Mindy Aisen, M.D., conducts research designed to maximize independence for patients by restoring lost function or decreasing the impact of disability. Research achievements range from new technology in the areas of amputation, spinal cord injury, vision impairment, and hearing loss to disabilities associated with aging. Recently, RR&D enhanced stroke therapy by being the first to demonstrate that robot-assisted neurorehabilitation is more effective than conventional treatment.

VA continues to focus on its mission of providing excellent health care for America's veterans. VA researchers have long played key roles in developing important health care innovations and are dedicated to keeping VA at the forefront of science and medicine. I am pleased to present this document highlighting some of their major recent achievements.

JOHN R. FEUSSNER, M.D., M.P.H.

DESIGNATED RESEARCH AREAS

AGING AND AGE-RELATED CHANGES

- ◆ NORMAL AGE-RELATED CHANGES
- ◆ AGING SYNDROMES (*FRAILITY, IMMOBILITY, FALLS*)
- ◆ COMPOUND PROBLEMS AND COMORBIDITIES
(*COEXISTING DIABETES AND CORONARY ARTERY DISEASE, DEMENTIA, HIP FRACTURE*)
- ◆ CARE OF ELDERLY VETERANS
- ◆ END OF LIFE ISSUES

ACUTE ILLNESS AND TRAUMATIC INJURY

- ◆ AMPUTATION (*DUE TO INJURY OR DISEASE*)
- ◆ BONE FRACTURES AND JOINT INJURIES
(*REPAIR AND REPLACEMENT*)
- ◆ (*TRAUMATIC*) BRAIN INJURY
- ◆ MULTI-ORGAN FAILURE
- ◆ SHOCK (*SEPSIS*)

MILITARY AND ENVIRONMENTAL EXPOSURES

- ◆ EMERGING PATHOGENS
- ◆ POST-TRAUMATIC STRESS DISORDER (*PTSD*)
- ◆ PSYCHOLOGICAL STRESS (*VIOLENCE, SEXUAL ABUSE*)
- ◆ THERMAL EXPOSURE (*BURNS, HYPOTHERMIA*)
- ◆ TOXINS AND IRRITANTS (*DERMAL, REPRODUCTIVE, RESPIRATORY*)

CHRONIC DISEASES

- ◆ BONE AND JOINT DISORDERS (*CHRONIC LOW BACK PAIN, OSTEOARTHRITIS / OSTEOPOROSIS*)
- ◆ CANCERS (*ADULT LEUKEMIA / LYMPHOMA, SOLID TISSUE TUMORS, CANCER PAIN*)
- ◆ CARDIOVASCULAR, CEREBROVASCULAR, PERIPHERAL VASCULAR DISEASES (*MYOCARDIAL INFARCTION, STROKE, HEART FAILURE*)
- ◆ CHRONIC INFECTIOUS DISEASES (*HIV / AIDS, HEPATITIS*)
- ◆ CHRONIC LUNG DISEASE
- ◆ CHRONIC RENAL DISEASE
- ◆ DEMENTIA & NEURONAL DYSFUNCTION (*ALZHEIMER'S AND PARKINSON'S DISEASE*)
- ◆ DIABETES & MAJOR COMPLICATIONS
- ◆ GASTROINTESTINAL DISORDERS (*BOWEL AND LIVER DISORDERS*)
- ◆ SPINAL CORD INJURY & REGENERATION

SENSORY DISORDERS AND LOSS

- ◆ HEARING DISORDERS
- ◆ VISION DISORDERS
- ◆ DISORDERS OF TASTE AND SMELL

MENTAL ILLNESS

- ◆ ANXIETY DISORDERS
- ◆ BEHAVIORAL DISORDERS
- ◆ DEPRESSION AND MOOD DISORDERS
- ◆ SCHIZOPHRENIA
- ◆ SPECIALIZED VA MENTAL HEALTH SERVICES
(*BEHAVIORAL AND MEDICAL INTERVENTIONS*)

SUBSTANCE ABUSE

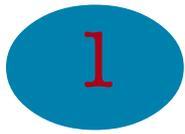
- ◆ ALCOHOL
- ◆ DRUG
- ◆ TOBACCO
- ◆ DUAL DIAGNOSIS (*ALCOHOL AND DRUGS*)
- ◆ SPECIALIZED SUBSTANCE ABUSE SERVICES
(*BEHAVIORAL AND MEDICAL INTERVENTIONS*)

SPECIAL (UNDERSERVED, HIGH RISK) POPULATIONS

- ◆ VETERANS WITH PERMANENT DISABILITIES
(*BLIND AND PARALYZED*)
- ◆ VETERAN COHORTS DEFINED BY SHARED MILITARY EXPERIENCE (*PRISONERS OF WAR, PERSIAN GULF VETERANS*)
- ◆ HISTORICALLY UNDERSERVED VETERANS
(*WOMEN, RACIAL, ETHNIC, CULTURAL MINORITIES, RURAL VETERANS*)
- ◆ VETERANS WHOSE LIVING ARRANGEMENTS POSE CHALLENGES TO THEIR HEALTH (*HOMELESS, HOMEBOUND*)

HEALTH SERVICES AND SYSTEMS

- ◆ SUPPLY AND ORGANIZATION OF RESOURCES & SERVICES
- ◆ DELIVERY / COORDINATION OF RESOURCES & SERVICES
- ◆ OUTCOMES OF CARE



AGING AND AGE-RELATED CHANGES

Research in this area represents VA's efforts to identify the unique characteristics of the aging process and develop strategies to treat or prevent age-related health problems. Scientists have focused, for example, on the special nutritional needs of older adults, treatment and prevention of frailty, immobility and falls, and end-of-life issues. Following are a few examples of our recent research achievements in this area.

Post-stroke rehabilitation guidelines improve patient outcome

Stroke is one of the most costly, disabling, and deadly diseases. Stroke guidelines have been created to assist clinicians in providing standards for acute and post-acute care. These guidelines, however, have never been evaluated for their effect on patient outcomes. This observational study of nearly 300 patients for six months showed that complying with post-stroke guidelines has a positive effect on functional outcomes and patient satisfaction. Study results also show that guideline compliance was significantly higher for veteran patients who received inpatient post-acute rehabilitation in VA rehab units or non-VA acute rehabilitation settings compared to patients who received post-acute care in nursing homes. These findings support the use of guidelines to assess quality of care and improve outcomes. *Health Services Research and Development*

Hoenig H, Sloane R, Horner RD, Zolkewitz M, Duncan PW, Hamilton BB. A taxonomy for classification of stroke rehabilitation services. Archives of Physiology and Rehabilitation, 81(7):853-62, July 2000.

Reker DM, Hoenig H, Zolkewitz MA, Sloane R, Homer RD, Hamilton BB, Duncan PW. The structure and structural effects of VA rehabilitation bed service care for stroke. Journal of Rehabilitation Research and Development, 37(4):483-91, Jul-Aug 2000.

Age-associated memory loss may be reversible

A VA team and colleagues have identified a process by which the normal primate brain degenerates with aging and showed that this degeneration can be reversed by gene therapy. In a study of normal monkeys, the researchers found that aging was accompanied by significant shrinkage and loss of function in nerve cells of the brain's cholinergic system, which regulates the brain's cortex and hippocampus, allowing the cortex to process information. Equally important, these nerve cells were not dead, only atrophied, and returned to nearly normal function and appearance after gene therapy that delivered nerve growth factor to the impaired cells. In addition to implications for cognitive function in normal aging, the findings also may offer a new approach against the cognitive decline in conditions such as Alzheimer's disease, in which this same system of cells degenerates and dies. *Medical Research Service*

Smith DE, Roberts J, Gage FH, Tuszynski MH. Age-associated neuronal atrophy occurs in the primate brain and is reversible by growth factor gene therapy. Proceedings of the National Academy of Sciences, USA, 96(19):10893-8, 1999.

Patients' preferences for life-sustaining treatment in advance directives

An HSR&D project demonstrated the critical need for more informed advance care directives that accurately reflect patient preferences regarding life-sustaining treatment and inform provider decisions. Studies show that physicians may undervalue patient quality of life when compared with the patient's own perceptions. In addition, physicians, nurses and spouses generally were unable to judge accurately what, in the patient's opinion, would constitute "futile treatment."

This HSR&D research resulted in the publication of an advance care planning workbook entitled *Your Life, Your Choices*, which is now available on the internet at <http://www.va.gov/resdev/programs/hsrd/ylyc.htm>.

This comprehensive workbook can be used to educate patients about advance care planning outside of the clinical setting. Exercises and other aspects of the workbook can promote meaningful communication between patients and proxies, facilitate efficient discussions between clinicians and patients, and guide future medical care in the event of decisional incapacity. Recommendations from this research have been distributed throughout the VA by the National Center for Clinical Ethics and at national meetings and conferences. The workbook's use in the VA health care system should improve the advance care planning process and advance directive completion rate in the VA. *Health Services Research and Development*

Pearlman RA, Starks HE, Cain KC, Rosengren D, Patrick DL. Your life, your choices - planning for future medical decisions: how to prepare a personalized living will. In: Pearlman RA, Starks HE, Cain KC, Rosengren D, Patrick DL, eds. Department of Veterans Affairs: Washington, DC, 1997.

Evaluation of geriatric evaluation and management (GEM) units

The proportion of veterans over age 65 will increase from 26 percent in 1990 to 46 percent in 2020, and VA must be prepared to serve the needs of this growing population. A large, multi-outcome study will determine whether specialized inpatient and outpatient units are the best way for VA to care for elderly patients. The impact of this study will extend far beyond VA, as millions of older Americans come under managed care. No other study is likely to provide the conclusive and incontrovertible evidence needed to guide policy in this critical area. *Cooperative Studies Program*

Evaluation of Geriatric and Management (GEM) Units and Geriatric Follow-up. CSP #6. Palo Alto.

Hospice study helps VHA improve end-of-life care

Increasing access to high-quality hospice services is an important element of VA's comprehensive strategy to improve care for

terminally ill veterans. The Veterans Hospice Care Study provides important information on how to achieve this goal. The final report, which was submitted to Congress, highlights the different programs through which hospice care is delivered in the VHA, describes patient and family satisfaction with care, and identifies barriers to obtaining hospice care. These results are serving as the focal point for efforts to improve end-of-life care throughout the VA delivery system. *Health Services Research and Development*

Hickey EC, Berlowitz, DR, Anderson, J, Hankin C, Hendricks, A, Lehner L. The veterans hospice care study: an evaluation of VA hospice programs. Final Report. February, 1998. Report Number MRR 97-004.

New resource guide provides information on VA's long-term care services

A new, three-volume Guide to Long-Term Care Data in the VA is helping clinicians, researchers and policymakers plan care and services for those veterans who need long-term care. Now available through HSR&D's Veterans Information Resource Center web at <http://www.virec.research.med.va.gov/DATABASES/LTCRGUID/EXPAGE.HTM>, this guide was developed after researchers conducted a thorough review of VA databases for long-term care. It identifies sources of data for research, as well as clinical use, and documents the limitations of these data. *Health Services Research and Development*



ACUTE ILLNESS AND TRAUMATIC INJURY

The field of acute and traumatic injury centers on injuries due to blunt force, temperature extremes, electric shock, pressure, or diseases such as diabetes and cancer. Specific focus areas within this field include amputation, bone fractures, brain injury, multi-organ failure, stroke, and shock. Researchers are also investigating the physical, psychological, cognitive and behavioral effects of acute and traumatic injuries, and the health services and procedures required to treat them.

VA and non-VA hospitals comparable for heart attack care

This study found care for acute myocardial infarction to be comparable among patients in VA and non-VA facilities. Despite the fact that VA patients were significantly more likely to have other chronic complications, such as hypertension, chronic obstructive pulmonary disease (COPD) or asthma, diabetes, stroke or dementia, there were no significant differences in 30-day or one-year mortality for those receiving VA and non-VA hospital care. These data suggest a similar quality of care for acute myocardial infarction for patients in VA and non-VA institutions. *Health Services Research and Development*

Petersen LA, Normand SLT, Daley J, McNeil, B. Outcomes of myocardial infarction in Veterans Health Administration patients compared with medicare patients. The New England Journal of Medicine, 343:1934-41, December 28, 2000.

Improving amputee mobility and independence

VA researchers in Seattle are developing new prosthetic limbs that will provide unprecedented mobility for veteran amputees. Many individuals with amputations across the shin or thigh lack endurance because of the extreme effort simply

to walk with today's prosthetic limbs. To combat this problem, researchers developed an artificial muscle and tendon to replace the lost musculature of the lower limb. The resulting powered prosthetic limb is expected to reduce patient fatigue and produce greater propulsive forces for walking. *Rehabilitation Research and Development*

Kllute GK, Hannaford B. Fatigue characteristics of McKibben artificial muscle actuators. Proceedings of the IEEEIRS7 1998 International conference on Intelligent Robotic Systems (IROS '98), Victoria BC, Canada, 776-1781, 1998.

Popular arthritis drugs proven dangerous for ulcer sufferers

A new class of painkillers, COX-2 inhibitors, used to treat arthritis may prove dangerous for some individuals. These drugs differ from conventional nonsteroidal anti-inflammatory drugs (NSAIDs) in that they block the enzyme involved in pain and inflammation (COX-2) and they do not harm the enzyme that protects the stomach (COX-1). However, recent VA research shows that these drugs may block the body's natural ability to heal stomach ulcers by inhibiting angiogenesis, the formation of tiny blood vessels essential to wound and ulcer healing. Researchers treated rat and human cells with indomethacin, a conventional NSAID or NS-398, a COX-2 inhibitor. Results showed a significant decrease in angiogenesis with the COX-2 inhibitor. *Medical Research Service*

Jones MK, Wang H, Peskar BM, Levin E, Itani RM, Sarfeh IJ, Tarnawski AS. Inhibition of angiogenesis by nonsteroidal anti-inflammatory drugs: insight into mechanisms and implications for cancer growth and ulcer healing. Nature Medicine, 5(12):1418-23, December 1999.

Improved design and function of upper limb prostheses

A VA research initiative involving microcomputer technology will modernize the design of electric-powered upper limb prostheses. VA researchers have developed a position-sensitive controller that will improve functional perfor-

mance, fitting flexibility, and ease of operation. The new controller provides sensory feedback from the prosthesis to the amputee, thus giving the amputee a better “feel” for the position of his prosthetic limb in space. This important research by VA will help assure better prostheses and better controllers for all upper-limb amputees. *Rehabilitation Research and Development*

Weir RF, Childress DS, Heckatborne CW. Towards achieving the goal of meaningful, coordinated, subconscious, multi-functional control of prostheses. Proceedings of the VA Rehabilitation Research & Development Service 1st Annual Meeting, “Enabling Veterans: Meeting the Challenge of Rehabilitation in the Next Millennium,” Washington, DC, 1998.

Bertos YA. The design and development of an embedded microcontroller system for an E.P.P. based position controller for upper-limb prostheses. Master’s Thesis, Department of Electrical Engineering, Northwestern University, 1999



MILITARY AND ENVIRONMENTAL EXPOSURES

Military and environmental exposures are a unique concern to veterans. Researchers working in this field are investigating the chronic health effects of events veterans experience during military service. This includes contact with foreign substances, such as toxins, irritants, or emerging pathogens, extreme temperatures, and post-traumatic stress disorder (PTSD). Gulf War veterans are a particular focus as we learn more about their special health concerns. Following are descriptions of selected studies in the areas of Gulf War veterans’ illnesses, PTSD, and infectious agents.

Amyotrophic lateral sclerosis (ALS) among Gulf War veterans

The Durham Epidemiologic Resource and Information Center is conducting an epidemiological investigation of the incidence of ALS (Lou Gehrig’s disease) among veterans of the Gulf War. The study is focusing in particular on three areas: defining the natural history of ALS; determining whether there is a higher-than-expected occurrence of ALS among Gulf War veterans; and ascertaining the possible or probable cause(s) of ALS if above normal event rates are determined.

Through a national survey of veterans and follow-up examinations, the study will increase the understanding of ALS among Gulf War veterans by developing descriptive epidemiology of cases. It will also compare the rate of ALS among Gulf War veterans with that of military personnel on simultaneous active duty but not deployed to the Gulf. Researchers are also investigating possible etiologic factors (with focus on environmental factors) in the Gulf and possible genetic-based susceptibilities to neurodegenerative disorders. *Cooperative Studies Program*

An investigation into the occurrence of ALS among veterans of the Gulf War. CSP# 500, Durham.

Testing antibiotic treatment for patients with Gulf War illnesses

VA researchers are testing a possible treatment for Gulf War illnesses (GWI). Although the cause of GWI is unknown, one explanation that has received fairly wide attention holds that infection with the microorganism *Mycoplasma fermentans* may be responsible. The purpose of this study is to determine the effectiveness of a one-year course of an antibiotic called doxycycline in patients with GWI who test positive for mycoplasma species. If doxycycline is shown to be effective, this relatively inexpensive and easily delivered drug could improve symptoms and possibly cure many veterans with GWI. *Cooperative Studies Program Collaborator: Pfizer Pharmaceuticals*

Antibiotic treatment of Gulf War illnesses. CSP #475, Perry Point

Multi-modal therapy in veterans with Gulf War illnesses

There is no definitive therapy for treating patients with Gulf War illnesses (GWI), and veterans suffering from this symptom complex are frequently frustrated by continued pain, fatigue or cognitive difficulties. VA researchers are trying to determine whether cognitive behavioral therapy and aerobic exercise, two approaches that have provided relief for people with fibromyalgia and chronic fatigue syndrome, can be used to help veterans with GWI. The study has enrolled more than 1,000 veteran patients in one of four treatment groups: cognitive behavioral therapy plus aerobic exercise, aerobic exercise alone, cognitive behavioral therapy alone, and usual and customary care. This research may provide needed answers for veterans who suffer from these mysterious and often disabling illnesses. *Cooperative Studies Program*

A randomized, multi-center, controlled trial of multi-modal therapy in veterans with Gulf War illness. CSP #470, West Haven

Group-treatment model for PTSD

Despite the often devastating effects of post-traumatic stress disorder (PTSD) on veterans, there is no proven, effective method to treat this condition. This randomized clinical trial will test what VA considers to be the most promising approach for treating PTSD, trauma focus group therapy (TFGT). This study is evaluating the efficacy of TFGT for treating PTSD symptoms and its effect on other psychiatric symptoms, functional impairment, physical health and utilization of medical and mental health services. If this intervention is found to be effective and feasible, VA will have at least one proven therapy for veterans with this debilitating combat-related illness. *Cooperative Studies Program*

Group treatment of PTSD. CSP #420, Palo Alto

Flesh-eating bacteria studies point to better treatments

VA researchers have conducted landmark studies on the so-called “flesh-eating” group A streptococcal bacteria that can destroy body tissues and trigger fatal shock and organ failure. This team was the first to describe a group of patients who had suffered toxic shock syndrome caused by these strains of streptococci, the bacteria best known as the cause of strep throat. The researchers showed that toxins produced by these virulent strains cause the release of body chemicals that trigger the shock and organ failure. The team has also done critical work showing that penicillin, the antibiotic traditionally used to treat group A streptococcal infections, is ineffective against the flesh-eating strains and that patients must be treated with antibiotics that suppress toxin production.

Medical Research Service

Stevens DL, Bryant AE, Hackett SP, Chang A, Peer S, Kosanke S, Emerson T, Hinshaw L. Group A Streptococcal bacteremia: the role of tumor necrosis factor in shock and organ failure. Journal of Infectious Diseases, 173(3):619-26, March 1996.

Stevens DL. The flesh-eating bacterium: what's next? Journal of Infectious Diseases, 179;Suppl 2:S366-74, March 1999.

VA research focuses on the range of chronic diseases and conditions that are highly prevalent among veterans, including life-threatening conditions and less severe problems that affect quality of life and the need for health services. The disease may be a primary ailment or a complication resulting from another disease. Specific areas of emphasis include bone and joint disorders, cancer, vascular diseases, chronic infectious diseases, lung and renal diseases, dementias, diabetes, gastrointestinal disorders, and spinal cord dysfunction. Below are short descriptions of VA research studies in some of these areas.

Optimal management of patients with HIV infection (OPTIMA)

VA's Cooperative Studies Program (CSP) has started a collaboration with the national health-research agencies for the United Kingdom and Canada, the UK Medical Research Council and the Canadian Institutes for Health Research.

The first study under the new partnership is a multi-drug strategy study designed to compare a "standard" treatment of three or four antiretroviral drugs to a "mega" treatment of five or more drugs in patients who have failed at least two "highly active" antiretroviral regimens. It is the first large-scale, multicenter, randomized controlled trial to compare the relative efficacy of the different therapeutic strategies. The overall goal is to prevent new or recurrent AIDS-related health events, such as pneumonia or death, through an optimal combination of drugs. A total of 1,700 patients will be randomized over a 2-1/2 year period at 75 medical centers in three countries. The use of multiple settings in different 'therapeutic cultures' will allow for generalizability of the findings and provide evidence that will facilitate management of HIV disease in this group.

The study will be coordinated by the VA West Haven CSP Coordinating Center and is set to begin in 2001. Lead investigators are located at the Bronx and Palo Alto VA medical centers, the University of British Columbia, Canada, and the London School of Hygiene and Tropical Medicine, U.K. *Cooperative Studies Program*

Major trial testing new vaccine against shingles

Shingles in older people is extremely painful and can be disabling. Shingles is caused by the herpes-zoster virus that causes chickenpox in young people. After chickenpox is treated, the virus remains dormant in the body until late adulthood, when it may reactivate and cause shingles. There is no effective treatment for people who suffer from shingles lasting more than a month, nor is there an effective method to prevent shingles.

This study is testing a promising new vaccine for its ability to prevent shingles or reduce its severity and complications. This randomized, controlled trial will enroll 37,000 older veterans for a minimum of three years. If the vaccine proves successful, it will supply a safe and cost-effective means for reducing the severe impact of shingles and its complications on the health of older veterans. *Cooperative Studies Program*
Collaborator: Merck Pharmaceuticals

Trial of Varicella vaccine for the prevention of Herpes Zoster and its complications. CSP #403 West Haven.

Effect of custom orthosis on foot kinematics and forefoot pressure distribution

Foot ulcers related to conditions such as diabetes pose significant problems to patients and a vexing challenge to health care providers. Gaining an understanding of potential causes of foot ulcers, including increased pressures across the forefoot, bony malalignment, and changes in relative motions between bones can lead to a more systematic approach to treatment and prevention of this problem. An experimental flatfoot model is being used to determine the effects of rigid

and compliant (flexible) orthoses on the movement of the foot. Computerized scans delineate the bone architecture of each foot and are used to create three-dimensional images for design of customized orthoses. Early results show that the rigid orthosis can correct eversion (outward turning) of three foot bones. *Rehabilitation Research and Development*

Sangeorzan BJ, Czerniecki JM. *Rehabilitation Research and Development Center for Amputation, Prosthetics, Limb Loss Prevention*, 2000.

HEART DISEASE

Rise in 'good' HDL cholesterol vs. heart disease and stroke

The health benefits of reducing high levels of 'bad' low-density lipoproteins (LDL) are widely known. VA researchers, however, have completed the first large-scale clinical trial to show that raising 'good' HDL cholesterol levels (high-density lipoproteins) reduces the risk of heart disease and stroke. A VA Cooperative Study involving 2,531 men at 20 VA medical centers found that the drug gemfibrozil caused a 6 percent increase in 'good' HDL cholesterol in comparison to a placebo. In addition, the medication reduced coronary heart disease death by 22 percent, nonfatal heart attacks by 23 percent, and stroke by 29 percent.

The finding is particularly encouraging because gemfibrozil is safe, economical, and available as a generic drug. The study results offer a new therapy for the 20 to 30 percent of coronary heart disease patients who do not have elevated 'bad' LDL levels but do have low levels of HDL. Results indicating the benefit of gemfibrozil are being considered for inclusion within the Joint VA/DoD Clinical Practice Guidelines for the management of lipidemia in the subset of patients with this lipid profile.

Cooperative Studies Program

Robins SJ, Collins D, Wittes JT, Papademetriou V, Deedwania PC, Schaefer EJ, McNamara JR, Kashyap ML, Hershman JM, Wexler LF, Rubins HB. *Relation of*

gemfibrozil treatment and lipid levels with major coronary events, VA-HIT: a randomized controlled trial. Journal of the American Medical Association, 285(12):1585-91, March 28, 2001.

Rubins HB, Robins SJ, Collins D, Fye CL, et al. *Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. The New England Journal of Medicine*, 341(6):410-8, August 5, 2000.

VA compares favorably with private sector in coronary angioplasty study

This quality-of-care evaluation showed that VA's tiered health care system produces excellent outcomes from high-tech cardiac procedures, compared with the private sector. In this study of coronary angioplasty patients, VA patients experienced no difference in hospital- or 30-day mortality compared with private-sector patients, even though the VA patients had more complicated conditions. In addition, VA patients underwent less bypass surgery (sometimes a complication of angioplasty) within 30 days of the angioplasty procedure. *Health Services Research and Development*

Ritchie JL, Maynard C, Chapko MK, Every NR, Martin DC. *A comparison of percutaneous transluminal angioplasty in the Department of Veterans Affairs and in the private sector in the State of Washington. Journal of the American College of Cardiology*, 31(9):1094-9, May 1, 1998.

Heart attack response findings offer hope for new treatments

Researchers from the San Diego VA Medical Center and the University of California at San Diego (UCSD) have discovered new information about the body's molecular response to hypoxia, a condition characterized by decreased oxygen levels in blood or tissue resulting from heart attack or closing of cardiac blood vessels. They successfully mapped the basic response period to these cardiac events, starting with the release of a protein (HIF-1) that stimulates the activation of blood-vessel-developing genes, and the progress of those genes in reparation of dam-

aged tissue. The findings may lead to the development of new therapeutic treatments that could diminish the severity of heart attacks. Possible therapeutic implications may include the development of new treatments in emergency cardiac care.

The researchers are now planning to evaluate whether doctors can decrease heart attack severity and the damage done to heart tissue by increasing HIF-1 levels in cardiac patients, either pharmacologically or by gene therapy. Other researchers are investigating the effect of decreasing HIF-1 levels in cancer patients, with the intention of diminishing oxygen supply to cancer cells thereby prohibiting their growth and proliferation. *Medical Research Service*

Lee SH, Wolf PL, Escudero R, Deutsch R, Jamieson SW, Thistlethwaite PA. Early expression of angiogenesis factors in acute myocardial ischemia and infarction. The New England Journal of Medicine, March 2, 2000.

CANCER

New study results may lead to cancer pain treatment

Researchers have opened the door to the development of novel therapies for treating severe pain in bone cancer patients. They showed that osteoprotegerin, a secreted decoy receptor that inhibits activity of bone-destroying osteoclast cells, also blocks behaviors indicative of pain in mice with bone cancer. Osteoprotegerin actions seem to result from inhibition of tumor-induced bone destruction that in turn inhibits the neurochemical changes in the spinal cord, possibly involved in generating and maintaining cancer pain.

Although advances in cancer detection and therapy have increased the life expectancy of cancer patients, more than one million patients suffer from cancer-related pain each year. Pain is the first symptom of cancer in 20-50 percent of all cancer patients and 75-90 percent in advanced or terminal cancer patients. Bone cancer most frequently results from breast, ovarian,

prostate, or lung cancer spreading to the bone. Progress in understanding and treating bone cancer pain will also provide insights into potential therapies for pains arising from soft tissue cancers.

Existing treatments for bone cancer pain can be ineffective, burdensome to administer, and accompanied by numerous side effects. Therapy for severe bone cancer pain nearly always involves morphine which, when given at doses required to the pain, induces unwanted side effects resulting in significant reduction in the patient's quality of life. *Medical Research Service*

Honore P, Luger NM, Sabino MA, et al. Osteoprotegerin blocks bone cancer-induced skeletal destruction, skeletal pain, and pain-related neurochemical reorganization of the spinal cord. Nature Medicine, 6(7):838, May 2000.

Colonoscopy may be best way to screen for colon cancer

Researchers at 13 VA medical centers found that a significant segment of an apparently healthy population showed signs of colon cancer. Using colonoscopy to examine the entire lining of the colon in 3,121 seemingly healthy people aged 50-75, 10 percent were found to have colon cancer or serious precancerous growths. In addition, at least one-third of these lesions would have been missed by sigmoidoscopy, a commonly used screening technique that reveals only the lower (distal) part of the colon's lining. The study is the first to directly compare exams limited to the distal colon with exams of the entire colon to determine possible additional benefits of colonoscopy screening in an asymptomatic group of patients. Researchers also found that colonoscopy appeared reasonably safe with few complications such as bleeding or reactions to sedation used to make patients more comfortable during the procedure.

Colorectal cancer is the second leading cause of cancer deaths in North America. It is marked by a premalignant phase in which growths called polyps develop in the colon lining. Not all polyps become cancerous, but those that progress to cancer typically develop abnormali-

ties that flag them as dangerous. In the U.S. alone, it is now estimated that 138,000 men and women will be diagnosed with colorectal cancer each year and about 55,000 will die from the disease. The findings from this study provide the basis for a more sensitive colon cancer screening test and earlier detection and treatment. *Cooperative Studies Program*

Lieberman DA, Weiss DG, Bond JH, Ahnen DJ, Garewal H, Chejfec G. Use of colonoscopy to screen asymptomatic adults for colorectal cancer. The New England Journal of Medicine, 343(3):162-8, July 20, 2000.

VA research suggests path to more effective breast cancer treatment

Retinoic acid, a radioactive iodide currently used in fighting thyroid cancer, may have a role in the fight against breast cancer. Researchers and colleagues from the Molecular Endocrinology Laboratory, VA Greater Los Angeles Healthcare System, suggest that there is a potential for retinoic acid to increase the uptake of radioiodine into certain breast cancers. They found that retinoic acid stimulated the production of a specific protein, the sodium/iodide transporter, responsible for the increased uptake.

Findings to date are specific only for breast cancer cells that were capable of reacting to estrogen. However, retinoic acid may also be useful in the diagnosis and treatment of other types of breast cancer. *Medical Research Service*

Kogai T, Schultz JJ, Johnson LS, Huang M, Brent GA. Retinoic acid induces sodium/iodide symporter gene expression and radioiodide uptake in the MCF-7 breast cancer cell line. Proceedings of the National Academy of Sciences USA, 97(15):8519-24, July 18, 2000.

Landmark prostate cancer trial will illuminate treatment options

The management of localized prostate cancer in older men has generated considerable debate due to the risks and potential benefits associated with different treatment options. Prostate cancer is the second most frequent cause of cancer deaths in men. Research shows patients' treatment preferences vary significantly, depending on the risk associated with

surgery, life expectancy, symptoms and tolerance for their symptoms. As a result, patient preference and experience are critical factors in making treatment decisions for prostate cancer.

Important questions remain concerning long-term outcomes for prostate cancer treatment. VA, in collaboration with the National Cancer Institute (NCI) and the Agency for Healthcare Research and Quality (AHRQ), is addressing these questions through a landmark study that compares the two most widely used treatment methods: radical prostatectomy, in which the prostate is surgically removed, and "watchful waiting" in which only the disease symptoms are treated. The Prostate Cancer Intervention Versus Observation Trial (PIVOT) is a 15-year randomized study involving 2,000 men from approximately 80 VA and NCI medical centers throughout the country. All patients will be followed for at least 12 years. The results will supply information on treatment-specific survival rates, complications and quality of life.

When completed, this study will provide more definitive answers on the best treatment for early-stage prostate cancer. If watchful waiting is as effective as surgery, millions of health care dollars could be saved every year by avoiding unnecessary surgery. On the other hand, results favoring surgery would highlight the need for early detection and treatment of this disease. *Cooperative Studies Program*

Collaborators: National Cancer Institute; Agency for Healthcare Research and Quality.

Wilt TJ, Brawer MK The prostate cancer intervention versus observation trial (PIVOT). Oncology, 11(8):1133-43, 1997.

NEUROLOGICAL DISORDERS

Award-winning research breaks important ground on human memory

Pioneering research by Larry R. Squire, Ph.D., winner of the 1994 Middleton Award, has shed new light on the nature and processes of memory, generating knowledge that may lead

to treatments for learning disabilities, Alzheimer's disease, and other neurological problems. Among the key questions for which Dr. Squire and his colleagues are providing critical answers are: What is memory? Where is it stored in the brain and how does it work? What happens to memory during normal aging and in disease or brain injury?

The research team has established that memory is made up of many systems, each supporting a different type of memory. This revolutionary concept has changed the direction of research in this field. Through a series of animal experiments, VA researchers discovered the medial temporal lobe system that controls one form of memory. Their research also provided the first proof that the human hippocampus is a critical component of the medial temporal lobe memory system and is essential for human memory.

In another recent study, Dr. Squire and his colleagues focused on how the human brain files information. Using functional magnetic resonance imaging, a scanning technique that measures activity in different parts of the brain, they found that the brain structures associated with categorization are different from those necessary for simple rote memory. [Medical Research Service](#)

Knowlton BJ, Mangels JA, Squire LR. A neostriatal habit learning system in humans. Science, 273(5280):1399-402, September 6, 1996.

Reber PJ, Stark CE, Squire LR. Cortical areas supporting category learning identified using functional MRI. Proceedings of the National Academy of Sciences, USA;95(2):747-50, 1998.

Clark RE, Squire LR. Classical conditioning and brain systems: the role of awareness. Science, 280(5360):77-81, 1998.

Larry R. Squire, Ph.D., VA San Diego Health Care System VA Merit Review, Medical Research Service

Robot-assisted arm movement helps stroke patients

Rehabilitation researchers are investigating the use of robot-assisted arm movement to promote neurologic recovery in persons weak on one side following a stroke. The new robotic system can assist shoulder and elbow movements in three-dimensional patterns encompassing a large portion of the person's range of motion. The user can guide movement of his/her weak arm by moving the opposite arm in the mirror-image pattern. A clinical trial with chronic stroke subjects compared an eight-week intervention of robot-assisted movement with a control intervention of equal intensity consisting of conventional therapy.

The results indicate that robot therapy is as effective as conventional therapy, and may even have advantages over conventional therapy. Persons who trained with the robot had greater strength gains than persons who received conventional therapy. Robots can potentially implement highly repetitive, labor-intensive exercises more efficiently than currently possible. This is especially relevant given recent evidence that highly repetitive exercises may promote neurologic recovery. Robots can also potentially provide new exercise modes not currently possible. The advanced sensor technology on the mirror-image motion enabler allows precise measurement of interaction forces and movement patterns during therapy. This data will lead to a better understanding of the role of therapy in promoting neurologic recovery following stroke.

[Rehabilitation Research and Development](#)

Burgar CG, Lum PS, Shor P, Van der Loos HFM. Development of robots for rehabilitation therapy: the Palo Alto VA/Stanford experience. Journal of Rehabilitation Research and Development, 37(6):663-73, November/December 2000.

Electromyographic imaging of muscle architecture

Understanding the way in which particular muscles produce force requires accurate knowledge of muscle architecture. Investigators in Palo Alto have developed a technique to study motor-unit architecture by analyzing electromyographic signals. Signals recorded, using a needle electrode during a moderate voluntary contraction, are processed to identify the action potential of each active motor unit in the vicinity of the electrode. Action-potential landmarks are then used to estimate the relative locations of each motor unit's neuromuscular and musculotendinous junctions.

The analysis of different muscles reveals a variety of architectural organizations, including different muscle-fiber lengths, single and multiple innervation zones, pennation, and intramuscular aponeuroses. This type of analysis promises to be useful for studying muscle structure in normal subjects and structural changes in aging and disease. *Rehabilitation Research and Development*

Lateva ZC, McGill KC. Estimating motor-unit architectural properties by analyzing motor-unit action potential morphology. Clinical Neurophysiology, 112(1):127-35, January 2001.

Narcolepsy may be due to loss of brain cells

A loss of brain cells that make a chemical called "hypocretin" may be responsible for narcolepsy, a debilitating, lifelong disease that causes patients to fall asleep uncontrollably during the day. Researchers at the Sepulveda VAMC found that human brains from narcoleptics had up to 95 percent fewer hypocretin neurons compared with normal brains. Although hypocretin has been linked by scientists to narcolepsy in animals, the cause of human narcolepsy remains unclear. Researchers believe the loss of hypocretin neurons may stem from an autoimmune attack by the body, or a sensitivity of the cells to certain environmental or biological toxins.

Current treatments focus on the use of amphetamines and other stimulant drugs to keep narcoleptics awake during the day. These treatments do not completely reverse symptoms and produce unwanted side effects. This research confirms the potential for new therapies aimed at restoring the hypocretin messaging system in the brain. *Medical Research Service*

Thannickal TC, Moore RY, Nienhuis R, Ramanathan L, Gulyani S, Aldrich M, Cornford M, Siegel JM. Reduced number of hypocretin neurons in human narcolepsy. Neuron, 27(3):469-74, September 2000.

Sodium channels in multiple sclerosis and pain

Rehabilitation researchers have identified a previously unknown dysfunction in neurons involved in multiple sclerosis (MS). They found that a specific sodium channel, the molecular "battery" that produces electrical impulses in nerve cells, occurs in cells of brains affected by MS but not in those without neurological disease. Their work could revolutionize the treatment of MS.

In related work, the researchers recently discovered that two molecules control the expression of sodium channels involved in the hyperexcitability of pain-signaling neurons that occurs following nerve and spinal cord injury. The researchers have found that particular sodium channels are prevalent in spinal sensory neurons and not present in significant levels in other types of nerve cells. Increased understanding of the roles of these channels may lead to improved treatments for chronic pain disorders of the nervous system. *Rehabilitation Research and Development*

Black JA, Dib-Hajj S, Baker D, Newcombe J, Cuzner ML, Waxman SG. Sensory neuron-specific sodium channel SNS is abnormally expressed in the brains of mice with experimental allergic encephalomyelitis and humans with multiple sclerosis. Proceedings of the National Academy of Science, USA; 97(21):11598-602, October 10, 2000.

Fjell J, Cummins TR, Fried K, Black JA, Waxman, SG. In vivo NGF deprivation reduces SNS express and TTSX-R currents in IB4-negative DRG neurons. Journal of Neurophysiology, 81:803-11, February 1999.

Fjell J, Cummins TR, Davis BM, Albers KM, Fried K, Waxman SG, Black JA. Sodium channel expression in NGF-overexpressing transgenic mice. *Journal of Neuroscience Research*, 57:39-47, July 1, 1999.

FES and gait function after stroke

Investigators at the Cleveland Functional Electrical Stimulation (FES) Center are studying functional neuromuscular stimulation (FNS) to improve gait following stroke. Investigators found that stroke patients with sensation tolerate implanted FNS treatment with no discomfort. Preliminary findings show that acute stroke patients treated with implanted FNS have improvements in muscle function, coordination, and gait function. In a companion study, stroke patients who had completed conventional rehabilitation and had reached a functional plateau were treated with FNS twice weekly for nine months, achieving significant improvement in muscle function and gait deficits over their pre-FNS status. *Rehabilitation Research and Development*

Daly JJ, Ruff RL, Haycook K, Strasshofer B, Marsolais EB, Dobos L. Feasibility of gait training for acute stroke patients using FNS with implanted electrodes. *Journal of Neurological Sciences*, 179(1-2):102-7, October 1, 2000.

Daly JJ, Ruff RL. Electrically induced recovery of gait components for older patients with chronic stroke. *American Journal of Physical and Medical Rehabilitation*, 79(4):349-60, July-August 2000.

Daly JJ, Debogorski A, Strasshofer B, Scheiner A, Kollar K, Marsolais EB, Ruff RL, Snyder S. Percutaneous electrode performance and use for restoration of gait in patients with stroke. *Journal of Rehabilitation Research and Development*, in press.

Seeking better treatments for Parkinson's disease

A landmark VA Cooperative Study clinical trial will assess the effectiveness of surgical implantation of deep brain stimulation (DBS) to reduce the symptoms of Parkinson's disease. DBS is a new promising alternative therapy for Parkinson's disease. It will be compared to the current standard surgical treatment, pallidotomy, where a small lesion is made in a portion of the brain called the globus pallidus. The goal of this

project is to compare these two treatments and determine the most effective brain site for DBS surgical intervention.

This study will be conducted at VA's six new Parkinson's Disease Research, Education, and Clinical Centers (PADRECCs) located in Houston, Philadelphia, Portland, Richmond, San Francisco, and West Los Angeles. These centers will enable top VA researchers, clinicians, and educators to better understand Parkinson's disease, develop more effective treatments and clinical care strategies for patients, and improve education for caregivers. The study will begin in 2001 and will be a prospective, randomized, multi-center trial. While treatments exist, there is no cure for this debilitating disease that is becoming a serious health problem in the United States. VA medical centers treat at least 20,000 Parkinson's disease patients each year.

Cooperative Studies Program

VA researchers discover genes involved in aging and Alzheimer's disease

VA is at the cutting edge of genetic research in human aging and Alzheimer's disease, the devastating brain disorder that afflicts over four million Americans. VA researchers were part of an international team that discovered the first human gene associated with aging, a major advance in efforts to understand aging and age-related diseases. In addition, VA researchers identified the gene that causes Werner's syndrome, a rare inherited disorder marked by premature aging. They also found that this gene normally directs the production of enzymes called helicases, which cells need to uncoil and reproduce DNA and perform other cell functions. The team's findings indicate that mutations affecting DNA are key to the aging process.

VA researchers have also identified a gene that plays a key role in development of Alzheimer's disease. This discovery may allow them to better understand how the disorder develops in people who carry this gene. More recently, a multi-center team of VA researchers found that a gene associated with the body's

regulation of immune response may trigger earlier onset of Alzheimer's symptoms.

VA investigators also identified a gene that causes a form of dementia characterized by tangles of long, string-like filaments identical to those found in the brains of Alzheimer's patients. Previously, these filaments were thought to be a consequence of Alzheimer's rather than a factor in the disease's progress. The investigators found that a mutated form of the so-called "tau" gene produces these long filaments and causes nerve cell death in patients with frontotemporal dementia. These findings point to the tau gene as a potential target for new Alzheimer's disease treatments. *Medical Research Service*

Yu CE, Oshima J, Fu YH, Wijsman EM, Hisama F, Alisch R, Matthews S, Nakura J, Miki T, Ouais S, Martin GM, Mulligan J, Schellenberg GD. Positional cloning of the Werner's syndrome gene. Science, 272(5259):258-62, April 12, 1996.

Payami H, Schellenberg GD, Zarepari S, Kaye J, Sexton GJ, Head MA, Matsuyama SS, Jarvik LF, Miller B, McManus DQ, Bird TD, Katzman R, Heston L, Norman A, Small GW. Evidence for association of HLA-A2 allele with onset age of Alzheimer's disease. Neurology, 49(2):512-8, August 1997.

Osteoporosis / Osteoarthritis

Working to understand and prevent osteoporosis

Researchers at the Little Rock VA Medical Center, supported under the Research Enhancement Awards Program (REAP), are advancing understanding of osteoporosis, a bone disease affecting more than 28 million Americans. Specifically, the multidisciplinary effort focuses on identifying the mechanisms of bone loss in patients with metabolic, orthopedic, and cancer-related diseases, and the development of novel therapies for their management. Six VA investigators, led by Stavros C. Manolagas, M.D., Ph.D., are combining expertise in geriatrics,

orthopedics, surgery, biochemistry and pharmacology. The REAP funds will also be used to create new training opportunities and to launch novel research initiatives that will translate basic research findings into clinical applications.

Medical Research Service

Jilka PL, Weinstein RS, Bellido T, Roberson P, Parfitt AM, Manolagas SC. Increased bone formation by prevention of osteoblast apoptosis with parathyroid hormone. Journal of Clinical Investigations, 104(4):439-46, August 1999.

Defective cartilage cells linked to osteoarthritis

Researchers have found that nitric oxide, a potentially harmful free-radical gas found in the body, can significantly disturb the ability of mitochondria to breathe and produce energy. Their data suggests that a cartilage cell's mitochondria (structures within cells that produce most of the energy necessary for general health and well-being) go through a type of power failure where they no longer produce energy to generate healthy cartilage. Therefore, calcium deposits are formed and the joints deteriorate. Little is known about the biological causes of the disease. Since osteoarthritic cartilage is chemically different from normal aged cartilage, the disease does not appear to be a result of aging itself.

Current VA research suggests the potential for new drugs aimed at preserving mitochondrial function in cartilage cells, thereby stemming joint deterioration. Osteoarthritis, also known as degenerative joint disease, is the most common form of arthritis. Symptoms include pain, stiffness, and inflammation in the joints. Treatment typically involves pain-relieving and anti-inflammatory drugs along with heat-therapy and exercise. This treatment alleviates symptoms but does not address the cause of the disease.

Medical Research Service

Johnson K, Jung A, Murphy A, Andreyev A, Dykens J, Terkeltaub R. Mitochondrial oxidative phosphorylation is a downstream regulator of nitric oxide effects on chondrocyte matrix synthesis and mineralization. Arthritis and Rheumatism, 43(7):1560-70, July 2000.

Mechanical stimulation gives human arthritic cartilage cells a boost toward health

Research at the VA Palo Alto Rehabilitation Research and Development Center has yielded new insights into the response of human osteoarthritic cartilage cells to physical force or pressure. As a joint surface is damaged by disease, a specialized form of the structural protein, collagen, is lost from the cartilage exposing the bone surface causing pain and reducing freedom of movement. Researchers at the Palo Alto Rehabilitation Research Center showed that a short daily application of hydrostatic pressure, followed by a period with no pressure, increased expression of molecules essential to formation of collagen. Future studies will try to determine which loading conditions produce the best responsiveness and to assess whether mechanical stimulation will provide a viable way to regenerate healthy cartilage in diseased joints. *Rehabilitation Research and Development*

Smith RL, Lin J, Kajiyama G, Shida J, Trindade MCD, Yerby S, van der Meulen MCH, Vu T, Hoffman AR, Schurman DJ, Beaupre GS, Carter DR. Hydrostatic pressure and cartilage repair; analysis of chondrocyte collagen gene expression. Transactions of the 18th Annual Meeting of the Society for Physical Regulation in Biology and Medicine, 1998.

New methods for analyzing densitometry results can improve osteoporosis diagnosis

Dual-energy X-ray Absorptiometry (DXA) is currently the method of choice for measuring bone density and identifying individuals with low bone mass and osteoporosis. Results can be misleading, however, because different-sized bones of the same density can produce different readings. Researchers at the VA Palo Alto Rehabilitation R&D Center have developed a simple method for adjusting DXA scans of the heel bone for bone size.

This new method provides an accurate determination of volumetric bone density. In addition, this group of researchers has developed a new DXA-based index for estimating fracture risk in normal and osteoporotic patients. These new methods have immediate clinical

applicability in helping to identify individuals at risk for osteoporotic fractures. *Rehabilitation Research and Development*

Wren TAL, Yerby SA, Beaupre GS, Carter DR. Interpretation of calcaneus dual-energy X-ray absorptiometry measurements in the assessment of osteopenia and fracture risk. Journal of Bone and Mineral Research, 15(8):1573-8, August 2000.

LIVER / KIDNEY DISEASE

Study launched for severe diabetes complications

A large-scale clinical trial may determine whether intensified blood-sugar control can prevent the major vascular complications that lead to most deaths, illnesses, and treatment costs for patients with type II diabetes. This is a seven-year VA study in collaboration with the American Diabetes Association and several pharmaceutical companies, including SmithKline Beecham, Novo-Nordisk, Aventis, KOS, and Roche Diagnostics. The study will be conducted at 20 VA medical centers and will enroll 1,700 patients with type II diabetes for whom standard drug therapy is no longer adequate. Patients will be followed for five years to assess rates of major macrovascular events, including heart attack, heart failure, stroke, amputations due to ischemia, surgery for coronary artery or peripheral vascular disease, and cardiovascular death.

Participants will receive either standard therapy or an intensive therapy that would involve higher doses of the same drugs. Standard therapy for type II diabetes includes sulfonylurea and insulin-sensitizing medications designed to lower blood-sugar levels and sensitize the body to naturally produced insulin. The intensive therapy will include medications, along with other antihyperglycemic drugs and insulin that will be added in steps. The risk for type II diabetes increases with age, with most cases developing after age 40. More than 18 percent of Americans over age 65 and more than one-fourth of the VA patient population have type II diabetes. *Cooperative Studies Program*

Cellular on-off switch provides new tactics against liver disease

VA researchers in San Diego have discovered a cellular pathway that may offer a way to encourage liver cell growth in people with liver damage or to block the growth of liver tumors. They found that a gene cloned in the laboratory was a powerful regulator of development when they stimulated mouse liver cells with a hormone known to trigger cell growth. The key step was a single change in the protein product of that gene.

This finding may also point the way to better artificial livers for people needing a transplant and may even suggest ways to restore lost cells in the brain and other tissues. The researchers now hope to learn more about the mechanics of the protein change so they can use it as an “on-off” switch for cell growth, possibly developing drugs or other techniques to flip that switch. *Medical Research Service*

Buck M, Poli V, van der Geer P, Chojkier M, Hunter T. Phosphorylation of rate serine 105 or mouse threonine 217 in C/EBP beta is required for hepatocyte proliferation induced by TGF alpha. Molecular Cell, 4(6):1087-92, December 1999.

VA researchers identify potential new kidney cancer treatment

VA researchers have identified a promising new treatment for kidney cancer. Using a laboratory-developed analog of somatostatin, a hypothalamic hormone that inhibits the release of growth hormone, scientists were able to target specific receptors on tumor sites and reverse cancer growth. Nobel prize winner Andrew V. Schally, Ph.D., M.D.H.C, of the New Orleans VA Medical Center and leader of the research group, described the compound as “a magic bullet” that scientists have been seeking for 100 years.

Researchers implanted two types of human renal cell carcinoma (RCC) tumors in mice, and injected them with an analog, AN-238, previously shown to be effective in the treatment of prostate cancer, breast cancer, and brain tumors. After five weeks of treatment, the volume of the two types of tumors had decreased

67.2 percent and 78.3 percent. The analog works by targeting receptors on the surface of RCC tumors, inhibiting and even reversing tumor growth.

This is the first application of the cytotoxic (cell-destroying) compound in RCC which is the most common form of kidney cancer. RCC is diagnosed in an estimated 28,000 Americans each year and nearly 12,000 people died from the disease in 1999. These latest findings represent a great stride toward treatment of a cancer that has been resistant to both chemotherapy and radiation and has a very low survival rate.

Medical Research Service

Plonowski A, Schally AV, Nagy A, Kiaris H, Hebert F, Halmos G. Inhibition of metastatic renal cell carcinomas expressing somatostatin receptors by a targeted cytotoxic analogue of somatostatin AN-238. Cancer Research, 1;60(11):2996-3001, June 2000.

Anti-anemia drug for dialysis patients may be administered subcutaneously

More than 90 percent of hemodialysis patients experience severe anemia. A new drug, recombinant human erythropoietin, is very effective at combating this anemia but it costs \$5,000 to \$10,000 per patient annually when administered intravenously. However, a randomized, multi-center trial by VA found that recombinant human erythropoietin can be administered just as effectively subcutaneously (under the skin), with a dosage reduction of 32 percent and no substantial increase in patient pain or discomfort. The Cooperative Studies Program is working with the Health Care Finance Administration to estimate potential savings to Medicare from subcutaneous administration of this new drug. *Cooperative Studies Program*

Collaborator: AMGEN Pharmaceuticals Kaufman JS, Reda DJ, Fye CL, Goldfarb DS, Henderson WG, Kleinman JG, Vaamonde CA. Subcutaneous compared with intravenous epoetin in patients receiving hemodialysis. Department of Veterans Affairs Cooperative Study Group on Erythropoietin in Hemodialysis Patients. New England Journal of Medicine; 339(9):578-83, August 27, 1998. CSP#392, Hines.

Transgene treatment for diabetes

Type I diabetes mellitus is usually followed by autoimmune destruction of cells in the pancreas, leading to insufficient insulin production. Diabetes is a natural candidate for treatment by gene therapy since clinical symptoms are caused by a decreased production of a single protein. Numerous studies have demonstrated that functional gene transfer is successful both in animals and in cell cultures. Attempts to regulate transgenic insulin production, however, have proven inadequate as the insulin secretion has been insufficient to normalize blood glucose or it has produced lethal hypoglycemia. This study has resulted in the design of a system where insulin gene therapy utilizes transcription to regulate hepatic production of transgenic insulin.

Effective and safe insulin gene therapy will require regulation of transgenic insulin secretion. Researchers at the Atlanta VA Medical Center have created a liver-targeted insulin transgene by engineering glucose responsive elements into a hepatic promotor containing an inhibitory insulin response sequence. They demonstrated the applications of this transgene for the treatment of diabetes mellitus in mice by administering a genetically recombined virus. Blood sugar levels were reduced and maintained after a substantial glucose load.

Medical Research Service

Thule PM, Liu JM. Regulated hepatic insulin gene therapy of STZ-diabetic rats. Gene Therapy, 7:1744-52, October 2000.



SENSORY DISORDERS

Humans rely on sensory perceptions to interact with and interpret their surrounding environment. Loss or impairment of a sense, such as sight or hearing, can be a traumatic event, causing mental and emotional anguish. VA researchers are working toward understanding the biological causes of sensory loss, restoring or improving lost function for affected individuals, and improving the health services and rehabilitation aids that are available. Below are examples of our research in vision, hearing, and neurologic recoveries.

Outcome measurement system for blind rehabilitation services

The measures developed in two VA Merit Review projects form the basis of the national database implemented by VA Blind Rehabilitation Service and Information Technology Service on Jan. 1, 2001. Items from the Satisfaction Survey and the Functional Outcomes instruments are being used by VA headquarters (VAHQ) to evaluate rehabilitation outcomes for Blind Rehabilitation Service. Reports on these measures are provided on a quarterly basis to all VA Blind Rehabilitation Centers as well as VAHQ for purposes of program evaluation.

Rehabilitation Research and Development

De l'Aune W, Welsh RL, Williams MD. Outcome assessment of the rehabilitation of people with visual impairment: a national project in the United States. Journal of Visual Impairment and Blindness, 95(5):281-91, 2000.

Improvement of visual function evaluations

The procedures developed in two VA projects using the scanning laser ophthalmoscope have challenged the prevailing clinical lore about preferred retinal locus (PRLs) characteristics (exact location of the retina) and scotoma characteristics (a blind spot or blind area within the normal bounds of vision). The results from

these projects have been incorporated into practice plans for vision rehabilitation.

The scanning laser ophthalmoscope has improved evaluation of visual function in people with impaired vision. In particular, it has enhanced the assessments including the relationship between basic eye movements and the ability to carry out complex tasks, the ability to find information in a visual field, and face recognition ability. Defining the relationship between visual function as assessed by the scanning laser ophthalmoscope and activities of daily living is refining diagnostic and training methods used in vision rehabilitation services.

Rehabilitation Research and Development

Schuchard RA, Fletcher D. Preferred retinal loci and the scanning laser ophthalmoscope, in "principles and practice of ophthalmology, Section: optics and low vision rehab", Kraut J, Azar D, section ed. Albert D, Jakobiec F, ed. Saunders, Philadelphia, 2000.

Schuchard RA. Evaluation of visual function, in "Selfstudy series: adult low vision rehabilitation," M. Warren ed., American Occupational Therapy Association Publications, Washington DC, 2000.

Popular hearing aids undergo scientific evaluation

Although they have been in use for decades, three popular types of hearing aids—accounting for 70 percent of the market—underwent their first rigorous scientific testing in a clinical trial by VA's Cooperative Studies Program and the National Institute on Deafness and Other Communication Disorders (NIDCD). Results of the study, conducted at eight VA medical centers, may enable doctors to help millions of Americans deal more effectively with hearing loss. The report shows that hearing aids substantially help users in both quiet and noisy situations.

Hearing loss is particularly prevalent among veterans, in part due to increased occupational exposure to loud noise on military bases. In 1999, 85,000 veterans were fitted for hearing aids at VA medical centers. Due to its expertise in audiology, the VA healthcare system was chosen as a partner in hearing-aid research by NIDCD, part of the National Institutes of Health.

Up to 28 million Americans—including about a third of those age 65 or older—have nerve-related hearing loss, which can often be helped by hearing aids. But only about 20 percent of those who can benefit from hearing aids wear them. One reason is that many primary-care doctors may not be fully informed on the benefits of hearing aids. Primary-care doctors will benefit from knowing that hearing aids are an effective treatment for many patients, especially those with mild to moderate hearing loss. *Cooperative Studies Program*

Larson VD, Williams DW, Henderson WG, Luethke LE, Beck LB, et al. Efficacy of 3 commonly used hearing aid circuits: A crossover trial. Journal of the American Medical Association, 284(14):1806-13, October 11, 2000.

6

MENTAL ILLNESS

VA research in mental illness focuses on cognitive conditions, from anxiety disorders and depression to advanced schizophrenia. Investigators have made great strides toward identifying the underlying causes of these disorders and are currently working to identify improved treatment methods and better health service systems to care for those with mental illness. Following are brief descriptions of important studies that illustrate VA's research in this important area.

Team management improves depression care

Depression is the second most prevalent medical condition in the VA and has an impact on function and quality of life that is worse than many other chronic physical conditions. Most depression treatment takes place in primary care where it continues to be under-detected and under-treated. This study of depression treatment adapted the collaborative care model for managing chronic illness to the VA primary care setting and compared the team care approach with traditional consult-liaison treatment. In the team model, psychiatrists, psychologists and social workers were assigned to a team that developed a treatment plan based on the initial assessment and provided the plan to the primary care provider. Primary care provider efforts were reinforced by patient education materials and brief social work phone calls to support patient adherence, address treatment barriers and monitor symptomatology.

Team care resulted in significantly greater improvement in depressive symptomatology and psychosocial function than the more traditional consult-liaison treatment without increasing outpatient visits. As more chronic conditions are treated in the primary care setting, using this model may improve patient outcomes at a reasonable cost. Its potential impact on care and

outcomes for depression and other chronic conditions could be great. *Health Services Research and Development*

Hedrick SC, Chaney EF, Liu CF, Felker BL, Bagala R, Paden GR. Process of care in innovative and traditional treatments for depression in VA primary care: reallocating resources. Presented at VA Health Services Research and Development Service Annual Meeting, Washington, DC, February 15, 2001.

Chaney EF, Hedrick SC, Felker BL, Liu CF, Paden GR, Hasenberg NM. Improving treatment for depression in primary care: alternate strategies. Presented at Society of Behavioral Medicine Annual Scientific Sessions, Seattle, WA. March 23, 2001.

Screening tool helps to identify depression

Major depression can have serious consequences, yet it often goes undiagnosed and untreated. VA physicians now have an effective two-question screening tool they can use in outpatient settings to help identify veterans with major depression. They also have a new awareness of the scope of the problem. Recent research shows that depression is prevalent among 14 percent of VA outpatients (excluding those with substance abuse problems, mania and/or psychosis). These findings have been widely disseminated to increase screening. *Health Services Research and Development*

Whooley MA, Avins AI, Miranda J, et al. Case-finding instruments for depression: two questions are as good as many. Journal of General Internal Medicine, 12(7):439-45, July 1997.

Award winning sleep studies may help mentally ill

Eminent sleep researcher Robert McCarley, M.D., Deputy Chief of Staff for Mental Health Services at the Brockton/West Roxbury VA Medical Center, won the 1998 William S. Middleton Award, one of VA's highest scientific honors. Recognized as an authority on REM (rapid eye movement) sleep, Dr. McCarley was honored for his important contributions to our understanding of sleep and dreaming. For example, he was the first to systematically develop quantitative methods for testing

hypotheses on cellular control of sleep states. He and his colleagues have identified control mechanisms for non-REM sleep and demonstrated that certain brain stem cells that use the neurotransmitter (chemical messenger between nerve cells) acetylcholine are critical for promoting REM sleep. In contrast, they found that other brain cells using the neurotransmitters serotonin and norepinephrine act to inhibit REM sleep. McCarley's work has helped set the stage for new approaches to sleep abnormalities, including sleep disruptions in psychiatric disorders. *Medical Research Service*

Porkka-Heiskanen T, Strecker RE, Thakkar M, Bjorkkum AA, Greene RW, McCarley RW. Adenosine: a mediator of the sleep-inducing effects of prolonged wakefulness. Science, 276(5316):1265-8, May 23, 1997.

Schizophrenia gene discovery

In a major breakthrough for understanding and treating schizophrenia, VA researchers have discovered a gene that plays a major role in schizophrenia and is linked to two physiological defects found in schizophrenics and their family members. In studies of nine families with multiple cases of schizophrenia, scientists learned that an inability to screen out irrelevant background noise, a common defect in schizophrenics, is linked to a specific gene that codes for a brain receptor activated by nicotine. This discovery may help explain why schizophrenics tend to be heavy smokers. Although well documented, the high incidence of smoking among schizophrenics had been overlooked as a possible link to the root of schizophrenia.

VA researchers tested subjects for the defect by subjecting them to repeated sounds while recording brain waves. Results showed that the defect is hereditary and is present in non-schizophrenic as well as schizophrenic family members. Using a variety of genetic techniques, the researchers traced the chromosomal location of the defective gene to the site of a specific nicotine receptor.

More recently, these investigators found that

a defect in eye movement tracking is linked to the same receptor. These findings of sensory defects linked to a specific neurotransmitter receptor could have major ramifications for schizophrenia treatment. Although inhaling nicotine activates the receptor and provides short-term relief for schizophrenics, the effect is too short-lived to be of treatment value. Researchers are now investigating the cause of the genetic malfunction and are collaborating with drug companies to identify potential drugs to bind the receptors. *Medical Research Service*

Freedman R, Coon H, Myles-Worsley M, Orr-Urtreger A, Olincy A, Davis A, Polymeropoulos M, Holik J, Hopkins J, Hoff M, Rosenthal J, Waldo MC, Reimherr F, Wender P, Yaw J, Young DA, Breese CR, Adams C, Patterson D, Adler LE, Kruglyak L, Leonard S, Byerley W. Linkage of a neurophysiological deficit in schizophrenia to a chromosome 15 locus. Proceedings of the National Academy of Sciences, USA, 94(2):587-92, 1997.

Study contributes to medication guidelines for schizophrenia management

Antipsychotic medication is an essential component of treatment for schizophrenia, the second most common discharge diagnosis in VA. Researchers studied the relationship between patient outcomes and the management of medication for schizophrenia. Results showed that 49 percent of patients receiving care through a VAMC or state psychiatric hospital were prescribed doses outside the range recommended by practice guidelines for schizophrenia. This study also showed that patients who were prescribed medication within practice guidelines had significantly less severe symptoms. Findings from this study have contributed to the selection of national performance measures for the VA that will improve the quality of medication management and better patient outcomes.

Health Services Research and Development

Kirchner JE, Owen RR, Nordquist C, Fischer EP. Diagnosis and management of substance use disorders among inpatients with schizophrenia. Psychiatric Services, 49(1):82-5, January 1998.



SUBSTANCE ABUSE

Research on substance abuse encompasses all types of addiction, including alcohol, nicotine, and other drugs. VA scientists are working to identify the underlying causes of abuse and addiction, and the subsequent treatment and rehabilitation methods that prove most effective. Research also includes efforts to understand the ramifications of substance abuse throughout the body, such as the liver disease resulting from alcohol abuse. Below are examples of progress in this critical area.

Probing the genetics of alcoholism

VA researchers are among leaders in research devoted to teasing out the complex interplay between heredity and alcoholism. For example, one VA team recently reported that genetically engineered mice without a certain cell receptor consumed less alcohol than unaltered mice. Mice without the dopamine D2 receptor, a cellular docking site for the brain chemical dopamine, consumed half as much alcohol as “wild type” mice. The study illustrates a technique in which particular genes influence substance abuse. Researchers use molecular methods to delete, or “knock out”, a suspect gene and then study the effect in the “knock out” mice. In an earlier study, the VA researchers discovered that mice without a gene containing the receptor for serotonin, consumed twice as much alcohol as unaltered mice.

Although they are just beginning to understand the role played by receptor subtypes in alcohol consumption, VA researchers indicate these studies may ultimately lead to new pharmacological treatments or gene therapies. The researchers caution scientists who study how genes affect behavior that genetically identical mice behave differently in seemingly identical tests at three separate laboratories. They emphasize that genetic manipulation and effects should be replicated cautiously before drawing conclusions, especially when there are slight results in behavioral differences.

Medical Research Service

Crabbe JC, Wahlsten D, Dudek BC. Genetics of mouse behavior: interactions with laboratory environment. Science, 284(5420):1670-2, 1999, June 4, 1999.

Phillips TJ, Brown KJ, Burkhart-Kasch S, Wenger CD, Kelly MA, Rubinstein M, Grandy DK, Low MJ. Alcohol preference and sensitivity are markedly reduced in mice lacking dopamine D2 receptors. Nature Neuroscience, 1(7):610-5, November 1998.

Youthful drinking linked to alcoholism in later years

Marc A. Schuckit, M.D., a world leader in the study of alcoholism, won the 1997 Middleton Award for more than 20 years of pioneering research on the importance of genetic influence in alcohol dependence. His innovative population studies have set the stage for exciting progress in efforts to identify genes that play a role in alcoholism.

In a landmark investigation, Dr. Schuckit and his colleagues tracked 453 men, starting when they were college students, for 10 years to determine the relationship between the initial effect of alcohol on a person and later alcoholism. The research team found that men who showed little reaction to alcohol as students were far more likely to become alcoholics 10 years later. Thus, being able to “hold one’s liquor” at age 20 was a warning sign for risk that clearly raises the possibility that genes controlling a person’s initial reaction to alcohol may contribute to later alcoholism.

These findings were instrumental in a decision by the National Institute on Alcohol Abuse and Alcoholism to invest almost \$5 million a year over 10 years in the six-center Collaborative Study on the Genetics of Alcoholism. Dr. Schuckit is among the principal investigators for this project, which is yielding important advances in the search for genes related to alcohol dependence.

Medical Research Service

Schuckit MA, Smith TL. An 8-year follow-up of 450 sons of alcoholic and control subjects. Archives of General Psychiatry, 53(3):202-10, March 1996.

Marc A. Schuckit, M.D., VA San Diego Health Care System and National Institute on Alcohol Abuse and Alcoholism.

Combination treatment helps smokers kick the habit

Smoking is a major problem among veterans, contributing to a variety of health problems, including arterial disease, heart disease, chronic lung disease, lung cancer, and other disorders. VA researchers have found that smokers who took mecamylamine orally and used a nicotine patch were more successful at quitting than smokers who used only a patch. In one study, participants who used the combination approach had a 40 percent smoking-abstinence rate after six months, compared with 15 percent among those who used a patch alone. In another study, 40 percent of subjects who used the combination before trying to quit were successful, compared with success rates of 10 to 20 percent among those who used a patch only, mecamylamine only, or a placebo.

When used with a nicotine patch, mecamylamine destroys the taste of tobacco and blocks brain receptors that help nicotine produce its pleasurable and addictive effects. The approach offers a new strategy against smoking addiction and its related health impacts. *Medical Research Service*

Rose JE, Behm FM, Westman EC. Nicotine-mecamylamine treatment for smoking cessation: the role of pre-cessation therapy. Experimental and Clinical Psychopharmacology, 6(3):331-43, August 1998.

Jed E. Rose, Ph.D., VAMC Durham, NC American Cancer Society

New pharmaceuticals to treat addictive disorders

The VA Cooperative Studies Program and the National Institute on Drug Abuse (NIDA) are working together to clinically test medications for substance abuse, alcohol abuse, and mental illness. The goal of this program is to support the development and subsequent marketing of new pharmaceutical entities to treat addictive disorders and certain mental illnesses. These are areas of research that have been under-represented in the pharmaceutical development and for which a high national priority has been set by the Congress.

This collaboration will consist of several projects, including seven current or completed studies. Three of the seven studies involve the

drug buprenorphine for the treatment of opiate-dependent patients. One of these studies tested the efficacy of a liquid formulation, while another studied the safety and efficacy of the combination drug buprenorphine/naloxone. Successful results of these studies are now being reviewed by the FDA. If the buprenorphine/naloxone combination is approved, it would allow a formulation that could be given in a take-home dosing form by physicians experienced in the treatment of opiate dependence, thus resulting in a third study in this area. There are currently 583 patients in their last year of follow-up at 38 test sites in New York, Florida, Illinois, Texas, California, and Washington.

Cooperative Studies Program

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SPECIAL POPULATIONS

Demographic, socioeconomic, and health risk factors distinguish some groups of veterans from the general population. The VA Office of Research and Development is ensuring that these groups are fairly represented in the research program. Veteran populations identified for special attention include veterans with permanent disabilities, veteran cohorts defined by shared military experience, minority veterans, and homeless, institutionalized or homebound veterans. Examples of VA's research in this area follow.

Teledermatology benefits veterans with limited access to health-care delivery

Digital images of visual information can be transmitted within telemedicine networks. This study compared the reliability for the diagnoses and management plans given by clinic-based examiners to those of consultants using digital imagery. Preliminary results show that dermatologists agree on their diagnoses of skin lesions equally well whether evaluating the patient in person or reviewing the digital image. In addition, investigators found diagnostic accuracy to be comparable among clinic-based and digital image examiners. This study suggests that the clinical use of digital imaging is an appropriate alternative for patients with limited access to adequate clinical care. *Health Services Research and Development*

Whited JD, Hall RP, Simel DL, Foy ME, Stechuchak KM, Drugge RJ, et al. Reliability and accuracy of dermatologists' clinic-based and digital image consultations. Journal of the American Academy of Dermatology, 41(5 Pt 1):693-702, November 1999.

Services needed for women veterans differ from those of men

Findings from an HSR&D study on the health status of women veterans who use VA ambulatory care services is helping VA plan

more comprehensive and appropriate services for this growing service population. Study results strongly suggest that resources needed to care for women veterans differ greatly from those needed to care for male veterans. As the number of women veterans seeking VA care continues to increase, this information is critically important for providing high quality care for this special population of VA users. *Health Services Research and Development*

Skinner KM, Furey J. The focus on women veterans who use Veterans Administration health care: the Veterans Administration women's health project. Military Medicine, 163(11):761-6, November 1998.

Case management expands access to services for homeless veterans

Case managed residential care for homeless veterans with substance abuse tended to shift service delivery from inpatient settings to less expensive outpatient settings, this HSR&D study found. This approach improved patients' access to care. It also improved short-term outcomes that were measured in terms of health care, employment, and housing, although these gains tended to diminish during the year following treatment. This information will inform VA administrators and clinicians about the need for ongoing community care to maintain gains achieved in the residential setting. *Health Services Research and Development*

Conrad KJ, Hultman CI, Pope AR, et al. Case managed residential care for homeless addicted veterans: results of a true experiment. Medical Care, 36:40-53, January 1998.

Functional electrical stimulation may assist patients with paraplegia

Functional Electrical Stimulation (FES) uses surgically implanted electrodes to activate paralyzed muscles. A consortium including the Cleveland VA Medical Center, Case Western Reserve University and MetroHealth Medical Center is producing promising results that have led to new applications and many advances in restoring function to paralyzed individuals.

Advances by VA in the implantation and

control of functional electrical stimulation (FES) walking systems hold great promise for patients with paraplegia. A research participant with paraplegia is now testing a new 16-channel system that allows him to exercise and walk in a limited area around his wheelchair. An implanted neuroprosthesis is helping individuals with high chest or low neck injuries to exercise their legs, stand, and perform standing transfers. Another FES device offers promise for improved bladder and bowel control for individuals with spinal cord injuries, giving them greater freedom and reducing the costs and inconvenience of bladder and bowel care.

FES is also helping patients with tetraplegia due to spinal cord injury to grasp and release objects with paralyzed hands. Researchers are developing and testing new hand-grasp systems that offer finer control and extend function to the elbow and forearm. Another type of implant stimulates the triceps muscle so that individuals with tetraplegia can reach overhead and grasp objects. These and other advances in FES may allow persons with paraplegia and tetraplegia to expand employment opportunities and work more independently. *Rehabilitation Research and Development*

Kobeti R, Triolo RJ, Uhlir J, Bier C, Wibowo M, Polando G, Marsolais EB, Davis JA, Ferguson Y, Sharma M. Implanted functional electrical stimulation system for mobility in paraplegia: a follow-up case report. IEEE Transactions on Rehabilitation Engineering (in press).

Triolo RJ, Bogie K. Lower extremity applications of functional neuromuscular stimulation after spinal cord injury. Topics in SCI Rehabilitation 5(1):44-65, 1999.

Wuolle KS, Van Doren CL, Bryden AM, Peckham PH, Keith MW, Kilgore KL. Satisfaction and usage of a hand neuroprosthesis. Archives of Physical Medicine and Rehabilitation, 80:206-13, 1999.

Peckham PH, Keith MW, Kilgore KL. Restoration of upper extremity function in tetraplegia. Topics in SCI Rehabilitation, 5(1):33-43, 1999.

Early treatment with corticosteroids reduces damage from SCI

More than one million Americans live with disabilities resulting from spinal cord injury. Crushing injuries of the spinal cord trigger a cascade of biochemical events that may cause more damage than the initial trauma. To counter this destructive cascade, VA investigators tested two corticosteroids, methylprednisolone and trilizad, in animals with spinal cord injuries. The results: animals that received either drug within eight hours following injury could regain up to 25 percent of their lost neurological function. Subsequent clinical trials in patients with acute spinal cord injury established that this early intervention can help reduce permanent damage, setting the standard for treatment of acute compression spinal cord injury. Further research by VA is underway on newer compounds that may further reduce the disability and medical care costs of these injuries. *Medical Research Service*

Giovanini MA, Reier PJ, Eskin TA, Wirth E, Anderson DK. Characteristics of human fetal spinal cord grafts in the adult rat spinal cord: influences of lesion and grafting conditions. Experimental Neurology, 148(2):523-43, 1997.

Tissue engineering to replace lost nerves

Tissue engineering (combining living cells with synthetic materials) holds promise for repair and regeneration of skin, bone, cartilage, nerve and essential organs. Researchers at the VA Palo Alto Rehabilitation R&D Center are recruiting patients who require grafting of nerves in the hand, arm or leg. Rather than performing a whole-nerve autograft, the investigators will repair the damage with an artificial graft seeded with the patient's own cells from the sheath surrounding the nerve fibers. New biomaterials and techniques now being tested for reconstructing peripheral nerves may be applied to the more difficult problem of regeneration of the central nervous system after stroke or spinal cord injury. *Rehabilitation Research and Development*

Sabelman EE, Hu M. 3-Dimensional collagen strands promote Schwann cell proliferation & orientation. *Proceedings of the Biomedical Engineering Society 1998 Annual Fall Meeting, Cleveland, OH, Oct 10-13, 1998, paper no. TE. 14, Annals of Biomedical Engineering v. 26, Suppl. 1, p. S-137, Sept/Oct, 1998.*

Transplantation of myelin-forming cells to the injured CNS

Researchers in West Haven are studying the transplantation of Schwann cells as a treatment method for injury to the central nervous system (CNS). Using magnetic resonance imaging, the investigators hope to establish whether cells transplanted into the primate CNS can produce myelin, a complex protein that makes up the sheath. Myelinated nerves have found to conduct impulses more rapidly than those without myelin.

These studies serve as a necessary prelude to human studies that may lead to successful cell transplantation as a treatment for injury to the CNS. Investigators have also successfully developed cell harvesting and preservation techniques that will further research on transplantation of myelin-forming cells. *Rehabilitation Research and Development*

Kato T, Honmou O, Uede T, Hashi Y, Kocsis JD. Transplantation of human olfactory ensheathing cells elicits remyelination of demyelinated rat spinal cord. GLIA (in press).

Imaizumi T, Lankford AL, Kocsis JD. Transplantation of olfactory ensheathing cells or Schwann cells restores rapid and secure conduction across the transected spinal cord. Brain Research, 854(1-2):70-8, January 31, 2000.

Waxman SG, Kocsis JD. Experimental approaches to restoration of function of ascending and descending axons in spinal cord injury; the neurobiology of spinal cord injury. Kalb RG, Strittmatter SM, eds. Humana Press, 2000.



HEALTH SERVICES AND SYSTEMS

Health Services and Systems is a research effort focused on improving the health care provided to our nation's veterans, whether it be for a specific disease or a broad category of care, such as primary or mental health care. Research in Health Services and Systems addresses supply and organization of resources and services, evaluation of treatment methods, health and safety of research participants, application of research findings to standard practice, and outcomes of care. The studies described below are part of our effort to ensure that our veterans receive the best possible care.

VA home health care increases satisfaction for patients, caregivers

An innovative model of home health care used by Department of Veterans Affairs (VA) hospitals—featuring a greater hands-on role for doctors and close cooperation among nurses, social workers and other team members—was found to yield more satisfaction for patients and family caregivers than private-sector home care.

In a study of nearly 2,000 home-care patients, most of them severely disabled or terminally ill, researchers from VA, the University of Illinois at Chicago, and Northwestern University tested VA's "Team-Managed Home-Based Primary Care" model against non-VA home-care at 16 sites. While death rate and physical functioning did not differ between the two groups of patients, VA patients and their caregivers overall expressed more satisfaction with their care. Terminally ill patients in the VA sample gave higher marks to their care in six of eight quality-of-life measures, including emotional functioning, bodily pain and mental health. Caregivers in the VA group reported less "burden," translating into reduced caregiver stress and burnout.

The study is among the first large-scale evaluations of home care to consider the burden

on family members and their emotional well-being. Previous research has shown that informal home-based family caregiving costs the nation nearly \$200 billion per year, compared to around \$30 billion for formal home health care. *Cooperative Studies Program*

Hughes SL, Weaver FM, Giobbie-Hurder A, Manheim L, Henderson W, Kubal JD, Ulasevich A, Cummings J. Effectiveness of team-managed home-based primary care. Journal of the American Medical Association, 284(22):2877-85, December 13, 2000.

Enhancing the quality of informed consent (EQUIC)

Informed consent is the keystone of the protection of human rights in medical research, along with careful review of proposed projects. EQUIC is a Cooperative Studies program-wide project aimed at systematically improving the quality of informed consent, by testing and measuring the results of innovative approaches to informed consent. Practitioners of clinical trials must ensure that patients' participation in research is informed and voluntary. This responsibility suggests that researchers should strive continuously to improve the effectiveness of methods for informing prospective research volunteers about experimental studies, thereby enhancing the protection of their interests.

EQUIC will test a method to assess the capacity of a research volunteer to understand and consent to a study; a method for "tailoring" an informed consent encounter to the vulnerabilities uncovered by that assessment; and a direct assessment of the success of an informed consent process at producing a good result, defined in terms of the successful protection of the patient's rights. Once these are fielded and tested, it will be possible to study a wide range of innovations in informed consent in the full variety of patients studied in the Cooperative Studies Program. An important side benefit will be the ability to assess the true results of current practice in the VA CSP, and, potentially, other systems. *Cooperative Studies Program*

Enhancing the Quality of Informed Consent (EQUIC) CSP # 476, Palo Alto.

VA utilization and survival rates

An observational study focusing on nine medical conditions examined patient utilization and survival rates during a three-year period that included a major VA organizational shift from inpatient care to ambulatory care. Results of the study indicate improved access to outpatient services. While inpatient care dramatically declined and utilization of outpatient care increased (except urgent care), survival rates improved or remained the same. Thus, the major reorganization of the VA health care system during the 1990s does not appear to be associated with any deterioration in patient survival rates. Study findings also showed an unexplained geographic variation in both utilization and outcome rates across all 22 VA health care networks that warrants further research to ensure equal care and accessibility for veteran patients across the country. *Health Services Research and Development*

Ashton C, Petersen N, Soucek J, Menke T, Collins T, Wray N. Changes in mortality, utilization, and quality in the Veterans Health Administration 1995-97, HCQCUS Technical Report 00-01. January 2000.

Community-based outpatient clinics provide equal care

Between 1995 and 2000 VA opened 242 new Community Based Outpatient Clinics (CBOCs) to allow more convenient access to care for veteran patients. A CBOC may be a VA operated clinic or VA-funded/reimbursed health care facility that is separate from the main VA medical facility. A study evaluated the performance of CBOCs including the provision of preventive and other health care, as well as patient access to care, utilization, cost and satisfaction.

Findings showed that on most measures CBOCs' performance was equivalent to their affiliated VA medical center, while on average, the total cost of health care was considerably lower for CBOC patients. Study results also indicate a few areas that warrant attention, such as CBOCs having fewer eye examinations for patients with diabetes and higher cost per primary visit, fewer specialty visits, and fewer

hospitalizations on average for all patients. This study will help VA continue to develop more effective, inclusive and accessible health care at the many CBOCs located across the country.

Health Services Research and Development

Chapko MK, Hedeem A, Maciejewski M, Fortney J, Borowsky SJ (Management Decision and Research Center, HSR&D, Dept. of Veterans Affairs). *CBOC Performance Evaluation: Program Implications and Future Performance Measures. Report No.1. March 1, 2000.*

Maciejewski M, Hedeem A, Chapko MK, Fortney J, Borowsky SJ. (Management Decision and Research Center, HSR&D, Dept. of Veterans Affairs). *CBOC Performance Evaluation: Performance Report 2: Cost and Access Measures. Report No.2. March 1, 2000.*

Clinical guidelines reduce pressure ulcer rates in nursing homes

Pressure ulcers are a common medical problem associated with considerable morbidity, particularly for patients with long-term care needs such as those in nursing homes. Practice guidelines on the prevention of pressure ulcers have been widely disseminated, and these guidelines have been successfully implemented in some VA nursing homes. Investigators studied 36 VA nursing homes to identify how these facilities accomplished successful implementation so that pressure ulcer care may be improved system-wide. Findings show that organizational features that promote the implementation of clinical guidelines include a culture that promotes innovation and teamwork. A trend toward lower rates of pressure ulcer development was associated with quality improvement implementation. Information from this report assists VA in taking the appropriate actions to increase the adoption of clinical guidelines that result in improved patient care. *Health Services Research and Development*

Berlowitz DR, Bezerra HQ, Brandeis GH, Kader B, Anderson JJ. *Are we improving the quality of nursing home care? the case of pressure ulcers. Journal of the American Geriatrics Society, 48(1):59-62, January 2000.*

Berlowitz DR, Hickey EC, Young G, et al. *Improving nursing home care: importance of organizational culture and continuous quality improvement implementation.*

Abstract presented at the HSR&D Service 18th Annual Meeting, March, 2000. Washington, D.C.

Computerized reminders improve compliance with standards of care

VA researchers have found that computer prompts improve physician compliance with outpatient care standards. This large-scale study is the first to examine the effects of prompting physicians to follow a specified standard of care. Records were examined from 275 resident physicians at 12 VA Medical Centers with a total of 12,989 patients. Overall, doctors who received computerized reminders (CRs) had higher rates of compliance for all standards of care.

Researchers selected 13 standards of care that would be widely accepted and could be implemented using the existing hospital database. Standards of care focused on patient conditions, such as coronary artery disease, hypertension, diabetes, atrial fibrillation, myocardial infarction, and gastrointestinal bleeding. A computerized software program was developed to download the information obtained from patients' visits during this study and compared to the hospitals' prescribed treatments and prescriptions. The program then determined whether the participants received proper care.

Although the study indicates the computer reminders improve compliance with multiple standards of care, enthusiasm and use of the CRs declined during the study. The authors noted that one possible explanation for this decrease may be that competing demands on the residents' time in busy clinics lead to neglect of CRs over time. Further research is needed to study causes of the physicians' decrease in use of the computerized reminders and ways to keep compliance at a high level. *Health Services Research and Development*

Demakis JG, Beauchamp C, Cull WL, Denwood R, Eisen SA, Lofgren R, Nichol K, Woolliscroft J, Henderson WG. *Improving residents' compliance with standards of ambulatory care: results from the VA Cooperative Study on Computerized Reminders. Journal of the American Medical Association, 283(11):1411-6, September 20, 2000.*

Surgical quality at VA improves since implementation of NSQIP

The quality of surgical care at VA hospitals has improved significantly since the inception of the National VA Surgical Quality Improvement Program (NSQIP), a collaborative effort of HSR&D and VA's Office of Quality Management. The 30-day mortality rate after major surgery was found to decline by nearly 10 percent. The rate of postoperative complications decreased by 30 percent.

Better surgical and anesthesia techniques, improved supervision of residents in surgical training, and improvements in technology and equipment have contributed to VA's progress in surgical care. The NSQIP has been instrumental in identifying ways to improve surgical care. The project researchers gathered data from 123 VA medical centers on patient-specific factors that affected post-surgical mortality and morbidity. These data enable the researchers to differentiate high-quality from low-quality facilities and to identify best practices to improve care. NSQIP researchers also studied functional outcomes of veterans who undergo major surgery in urology and orthopedics in 14 VA medical centers. They also collaborated with four affiliated academic health centers to implement the NSQIP at non-VA hospitals. *Health Services Research and Development*

Daley J, Forbes M, Young G. et al. Validating risk-adjusted surgical outcomes: site visit assessments of process and structure. Journal of the American College of Surgeons, 185(4):341-51, October 1997.

Khuri SF, Daley J, Henderson W, et al. The National Veterans Surgical Risk Study: a risk adjustment for the comparative assessment of the quality of surgical care. Journal of the American College of Surgeons, 180(5):519-31, May 1995.

Study shows black patients admitted to VA hospitals have lower mortality rates

Study results indicate that black patients admitted to VA hospitals with common medical diagnoses have lower mortality rates than white patients. This study, using data provided by VA's Health Services Research and Development Service Center for Quality of Care and

Utilization Studies in Houston, examined racial differences in mortality among more than 35,000 patients admitted to 147 VA hospitals. Thirty-day mortality rates for patients who were admitted with one of six common medical diagnoses (pneumonia, angina, congestive heart failure, chronic obstructive pulmonary disease, diabetes, and chronic renal failure) were compared. Study findings show that 30-day mortality was lower among blacks than whites for each of the six medical diagnoses, and that black patients also had lower in-hospital and 6-month mortality rates. This survival advantage is not readily explained, however it may reflect the benefits of equal access to health care and the quality of inpatient treatment at VA medical centers. *Health Services Research and Development*

Jha AK, Shlipak MG, Hosmer W, Frances CD, Browner MS. Racial differences in mortality among men hospitalized in the Veterans Affairs Health Care System. Journal of the American Medical Association, 285(3):297-303, January 17, 2001.