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*Chief Research and Development Officer*

## A Message from the Chief Research and Development Officer

The Cooperative Studies Program (CSP) comprises four Coordinating Centers (CSPCCs), a Clinical Research Pharmacy, and three Epidemiological Research and Information Centers (ERICs). CSP research results are influential in establishing new standards of care in a broad range of areas. By determining the effectiveness of novel or unproven therapies through multicenter clinical trials, research conducted through the CSP transforms medical science into medical services that directly benefit veterans thus, improving both survival and quality of life.

Recently, the CSP launched a major expansion of VA's clinical trials program with 22 large, multicenter trials on problems as diverse as heart disease, atherosclerosis, cardiac revascularization, heart failure, arrhythmia, pulmonary nodules, thromboembolism, hernia repair, post-traumatic stress disorder, schizophrenia, alcohol abuse, and substance abuse.

While CSP's research informs and shapes health policy and clinical practice in the VA, it often improves clinical practice strategies in the private sector as well. Here are just a few examples of how groundbreaking work by the CSP is answering critical clinical research questions that affect all Americans.

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## ■ Chronic Diseases

### **Heart Disease**

#### **Non-invasive approach works better at managing patients with non-Q-wave infarctions.**

Most patients who suffer a certain kind of heart attack known as a non-Q-wave infarction can be managed with a non-invasive approach that improves their survival and reduces treatment costs, according to results from VA's VANQWISH trial. This study evaluated two competing diagnostic and clinical care approaches in treating patients with non-Q-wave heart attacks. Under the conventional approach, coronary angiography is the essential first step, followed by additional non-invasive tests or therapeutic interventions. However, the invasive strategy is costly and poses additional risk to the patient. Alternatively, the patient may undergo a radionuclide ventriculogram and symptom-limited stress test, followed by whatever procedures are deemed necessary by the physician. This approach proved to reduce mortality, an unexpected and important finding. These results have significant implications, both for the improved survival of patients who suffer non-Q-wave infarctions and for avoiding unnecessary invasive procedures.

*Collaborator: Marion Merrell Dow Pharmaceuticals*

*Boden WE, O'Rourke RA, Crawford MH, et al. Outcomes in patients with acute non-Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy. The New England J Medicine; 338(25):1785-1792, 1998.*

CSP #368, Palo Alto

#### **Pivotal trial of digitalis in CHF treatment.**

Approximately 70 percent of patients with congestive heart failure (CHF) regularly use digitalis, despite the availability of newer treatments for CHF and despite controversy regarding the appropriateness of digitalis in treating CHF patients. CSP, in collaboration with the National Heart, Lung and Blood Institute, is conducting a major randomized trial to identify the role of digitalis in CHF treatment. With more than 300 participating medical centers in the U.S. and Canada, this was the largest international congestive heart failure trial ever conducted. It was also the first randomized

clinical trial on the effects of digitalis.

*Collaborator: Glaxo-Wellcome Pharmaceuticals; National Heart, Lung and Blood Institute (NHLBI)*

*The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. New England Journal of Medicine, 336(8):525-533, 1997.*

CSP #995, Perry Point

#### **Researchers evaluate use of beta-blockers for chronic heart failure patients.**

This major study, jointly funded by the National Heart, Lung and Blood Institute and the Intercardia Corporation, will determine whether beta-blockers extend the lives of patients with chronic heart failure. The implications of this trial, involving 2,800 patients with moderate to severe congestive heart failure, are substantial. In addition to prolonging patients' lives, researchers conservatively predict that the successful use of these drugs will save the VA system \$9.4 million a year.

*Collaborator: National Heart Lung & Blood Institute; Intercardia Pharmaceuticals*

*Beta-blocker Evaluation of Survival Trial.*

CSP #395, Palo Alto

#### **VA trial shows Gemfibrozil is cost-effective therapy for heart disease.**

Groundbreaking VA research demonstrated the effectiveness of the drug gemfibrozil in reducing coronary heart disease (CHD) among certain patients. About 25 percent of CHD patients have a lipid abnormality characterized by low HDL-cholesterol in the absence of high-risk LDL-cholesterol. The VA HIT study is the first trial to show significant reduction in the risk of major cardiovascular events by raising HDL, lowering triglycerides, and not changing LDL levels. HIT was a seven-year, double-blind trial comparing the use of gemfibrozil with a placebo in 2,531 men. Daily use of gemfibrozil reduced CHD risk by 22%, with significant reductions in CHD death, heart attack, stroke, and transient ischemic attacks. Gemfibrozil is now available off-patent and since there were no major adverse events associated with taking this drug, use of this medication is likely to reduce costs as well.

*The VA HDL Trial (HIT): Secondary Prevention of Coronary Heart Disease in Men With Low HDL-Cholesterol and Desirable LDL-Cholesterol.*

CSP#363, West Haven

### **A large-scale CSP study tests use of computers in exercise testing for heart disease.**

CSP researchers investigated whether computerized analysis of exercise testing improves the diagnosis of coronary artery disease (CAD). Exercise testing is the most commonly used tool to evaluate CAD in veterans. This study, the largest ever to be performed of exercise testing, enrolled more than 3,000 patients to determine whether computer technology improves upon standard visual analysis in predicting both the presence and severity of CAD. This study is expected to produce many benefits, including substantial reductions in unnecessary cardiac catheterizations, identification of patients who need coronary revascularization but have false-negative exercise tests, and major savings in Federal health care expenditures.

*Froelicher VF, Lehmann KG, Thomas R, et al. The electrocardiographic exercise test in a population with reduced workup bias: diagnostic performance, computerized interpretation, and multivariable prediction. Annals of Internal Medicine, 128(12):965-974, 1998*  
CSP #016, Palo Alto

### **FeAST study tests new theory on link between iron and arteriosclerosis.**

A major study by CSP will test a controversial new theory that excessive levels of iron in the blood leads to hardening of the arteries. Currently, iron is regarded as a nutrient that requires supplementation in the elderly. The Ferritin Adjustment Study (FeAST) will investigate the hypothesis that most adult men have too much iron in their blood. This surplus iron, the theory goes, promotes chemical reactions that cause arterial and venous plaques that block blood flow. If FeAST supports these conclusions, the results would have revolutionary implications for both circulatory diseases and human nutrition. For example, excess iron levels could be removed by regular blood donation, a safe and simple procedure.

*The Iron (Fe) and Atherosclerosis Study.*  
CSP #410, Palo Alto

### **Can warfarin prevent deaths from heart attack?**

About 1.5 million people in this country have a heart attack each year and 500,000 of them are fatal. Aspirin is commonly used to treat people with heart attacks. This VA study is evaluating whether giving people a blood thinner called warfarin in addition to aspirin will increase their chances for survival. Eight thousand

people will be followed for six years to determine whether this combination of drugs works better than aspirin alone.

*Collaborator: Dupont; Sterling-Winthrop Pharmaceuticals*  
Warfarin and Aspirin in Secondary Prevention Trial.  
CSP #387, West Haven

### **Study will evaluate two drugs in treatment of irregular heart beat.**

Atrial fibrillation (irregular heart beat) affects more than 1 million Americans and is responsible for 75,000 strokes a year. It is a risk factor for congestive heart failure, impairs the ability to exercise, and may produce disabling palpitations and other symptoms. The best approach to standardized therapy for atrial fibrillation remains uncertain. This study will compare two of the most promising agents – amiodarone and sotalol – to determine how effective they are in maintaining normal heart rhythm in patients with atrial fibrillation.

*Collaborator: Wyeth-Ayerst; Berlex Pharmaceuticals*  
The Effects of Antiarrhythmic Therapy in Maintaining Sinus Rhythm in Atrial Fibrillation.  
CSP #399, Hines

## **Cancer**

### **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. Yet, research shows that patients' treatment preferences vary significantly, depending on the risk associated with surgery, their life expectancy, their 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 Health Care Policy and Research (AHCPR), 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 expected management or "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. The treatment implications are substantial. If expected management 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.

*Collaborator: National Cancer Institute; Agency for Health Care Policy and Research*

*Wilt TJ, Brawer MK. The prostate cancer intervention versus observation trial (PIVOT). Oncology, 11(8):1133-1143, 1997.  
CSP #407, Perry Point*

### **New screening method may improve early diagnosis of lung cancer.**

Lung cancer is the leading cause of cancer death in the United States. Early detection of lung cancer greatly increases patients' chances for survival, which can be as low as 13 percent, up to 60 and even 90 percent. Current standard diagnostic technologies leave much to be desired. False negative rates are as high as 30 percent and false positive rates sometimes reach 40 percent for benign tumors. False positive results can lead to unnecessary surgeries. VA researchers are experimenting with a new screening approach that uses a type of imaging called 18-F-fluorodeoxyglucose (FDG) positron emission tomography (PET). Early experience with FDG-PET screening suggests that this method dramatically lowers and in some cases virtually eliminates false negative and false positive results. The development of a more accurate screening technique has the potential not only to save many lives but to prevent unnecessary surgeries as well.

*F-Fluorodeoxyglucose (FDG) Positron Emission Tomography (PET) Imaging in the Management of Patients with Solitary Pulmonary Nodules.  
CSP #027, Palo Alto*

### **Genetics may play role in development of aggressive prostate cancers.**

In this project, CSP researchers are examining the role genetics play in aggressive prostate cancer. CSP researchers believe that there is a genetic link to aggressive prostate cancer. They are investigating the importance of the length of a specific genetic sequence that regulates the initiation and growth of prostate cancer. Ultimately, the goal of this research is to reduce the number of prostate cancer deaths among veterans through earlier detection of the disease.

*Case-Control Study of Prostate Cancer in Black and White US Veterans.  
EPP #97-026, Durham*

### **Researchers focus on improving early detection of prostate cancer.**

VA researchers are searching for insights into interactions between genetic and environmental factors that affect prostate cancer, so that they can improve diagnosis of prostate cancer in veterans. Prostate cancer, the most commonly diagnosed cancer in American men, is especially high among African Americans. Results of this study are expected to improve survival among veterans who develop prostate cancer by more precisely identifying who is at risk for this disease and targeting screening efforts accordingly, which will increase early detection.

*Prostate Cancer Case-Control Study: Black vs. White: VA vs. Private Sector.  
EPP #97-024, Durham*

### **VA investigators search for colon cancer risk factors.**

Colon cancers are treatable if detected in time. Although there are methods for early detection of colon cancers or their precursors, adenomatous polyps, high costs make frequent mass screenings impractical. In this study, VA researchers are trying to determine what historical, environmental, and biological markers can identify patients at high risk for colon cancer. These patients would then be candidates for targeted screening programs. If successful, this research effort has major implications for reducing the mortality and suffering caused by colon cancer.

*Prospective Evaluation of Risk Factors for Large ( $\geq 1$  CM) Colonic Adenomas in Asymptomatic Subjects.  
CSP#380, Perry Point*



## Infectious Disease

### Disease staging helps determine treatment changes for HIV.

Findings from this study provide evidence-based guidance to physicians on when to change treatment for patients infected with HIV. VA researchers analyzed a method for measuring viral load and relating it to changes in disease development. They found that changes in patient blood values can predict illness. With that knowledge, physicians may determine proper treatment courses more efficiently and effectively.

*O'Brien W, Hartigan P, Daar ES, et al. Changes in plasma HIV RNA levels and CD4+ lymphocyte counts predict both response to antiretroviral therapy and therapeutic failure. [The Department of Veterans Affairs Cooperative Study Group on AIDS.] Annals of Internal Medicine, 126(12):939-945, 1997. CSP #298A, West Haven*

### Sepsis study demonstrates need for long-term treatments.

Severe sepsis, an infection in the bloodstream, is strongly associated with in-hospital mortality. Sepsis can cause death up to five years after hospitalization, according to a major study by VA researchers. The study also found that patients with sepsis who also have one or more malfunctioning organs, such as the heart, lungs, kidney, liver or brain, are more likely to die in the first year after infection. These results highlight the need for treatments addressing the long-term effects of sepsis, not just short-term, in-hospital effects. VA researchers are confident such treatments will save lives and reduce health care costs.

*Quartin A, Schein R, Kett D, et al. Magnitude and duration of the effect of sepsis on survival. JAMA, 277(13):1058-1063, 1997. CSP #209, West Haven*

### New flu vaccine may provide better protection for people with lung disease.

VA researchers are trying to determine whether a new vaccine can protect patients who have chronic obstructive pulmonary disease (COPD) against influenza and its often dangerous complications. COPD, a serious type of lung disease, is common among VA patients. COPD patients are especially vulnerable to developing severe complications from influenza that include pneumonia, hospitalization, and even death. The standard flu vaccine, given by injection in the arm, prevents flu in only about half of patients with COPD. Recently, a new flu vaccine that is sprayed in the nose has been de-

veloped. This VA study, a randomized, multi-center trial that involves 4,000 people with COPD, will determine whether patients who receive both flu vaccines are better protected than those who receive only the standard flu vaccine. Researchers started vaccinating patients in the fall of 1998 to observe whether they develop flu. If successful, this new immunization regimen will save lives, prevent serious complications, and reduce treatment costs. This study may have significant implications for changing VA policy on vaccinating individuals with COPD against flu.

*Collaborator: AVIRON Pharmaceuticals*

A Randomized, Controlled, Blinded, Multicenter Trial to Assess the Efficacy of Protection from Natural Influenza Virus Infection of Influenza Virus Vaccine, Trivalent, Types A and B, Live, Cold-Adapted (CAIV-T) and Inactivated Influenza Virus Vaccine in Patients with Chronic Obstructive Pulmonary Disease (COPD).  
CSP#448, West Haven

## Diabetes

### Implantable insulin pump shows good results in multi-center trial.

A large-scale, multi-center trial by CSP gives new hope for ending diabetic patients' need for daily insulin injections. Study results show substantial benefits from an implantable, computer-controlled insulin pump. Patients implanted with the pump had better blood sugar control, better weight control and significantly better quality of life. Congress asked CSP to evaluate the safety and efficacy of the implantable insulin pump in patients with adult-onset diabetes.

*Saudek CD, Duckworth WC, Giobbie-Hurder A, et al. Implantable insulin pump vs. multiple-dose insulin for non-insulin-dependent diabetes mellitus: a randomized clinical trial. JAMA 276(16):1322-1327, 1996. CSP #344A, Hines*

### CSP researchers investigate cost-effectiveness of diabetes screening.

A VA study of the cost-effectiveness of screening for diabetes mellitus may have wide implications for other health care systems that are trying to assess the impact of mass screening for this disease. VA researchers are looking at whether population-based screening for diabetes in non-pregnant adults yields better outcomes among these patients than diagnosis at a later, more symptomatic phase of the disease. One result of this study will be a better understanding of the short-term consequences of screening for diabetes

Additionally, as a supplement to this study, VA researchers are evaluating a new instrument for diagnosing diabetes by fluorescent scatter of the eye. If proven effective, this diagnostic tool will represent a significant advance over current diagnostic techniques because it is quick and non-invasive.

Screening for Diabetes Mellitus in Veterans.  
EPP #97-021, Durham

## ***Prostate Disease***

### **Some patients with benign prostate disease may benefit from watchful waiting.**

This major CSP trial concluded that watchful waiting may be an acceptable alternative to surgery for patients with moderate symptoms of benign prostate disease. The study was the first to compare transurethral resection of the prostate (TURP) in a controlled trial with a treatment strategy of watchful waiting. Prior to this study, considerable disagreement existed on whether the benefits of surgery outweighed the risks for men with moderate symptoms of prostate disease, and whether watchful waiting was a reasonable alternative. The results show that TURP is highly effective in relieving disease symptoms, with few complications or side effects. However, watchful waiting was also an effective treatment strategy for men who were able to cope with their symptoms and preferred not to have surgery.

Wasson JH, Reda DJ, Bruskewitz RC, et al. A comparison of transurethral resection to watchful waiting in men with moderate symptoms of benign prostatic hyperplasia. *New England Journal of Medicine*, 332(2):75-9, 1995.  
CSP #246, Hines

### **Study identifies optimal medical treatment for prostate disease.**

Enlarged prostate is a common problem in older men. This CSP study evaluated medications for the treatment of benign prostate disease, and found that one drug (terazosin) effectively relieved symptoms, while another drug (finasteride) did not. This landmark study defined the optimal medical treatment for benign prostate disease, providing older men with an effective alternative to surgery.

*Collaborator: Abbott; Merck Pharmaceuticals*

Lepor H, Williford WO, Barry MJ, et al. The efficacy of terazosin, finasteride, or both in benign prostatic hyperplasia. *Veterans Affairs Cooperative Studies Benign Prostatic Hyperplasia Study Group. New England Journal of Medicine*, 335(8):533-539, 1996.  
CSP #359, Perry Point

## ***Surgery***

### **NSQIP's new risk factor models help predict patient outcomes.**

Risk factor models developed by the National VA Surgical Quality Improvement Program (NSQIP) can predict hospitals that provide superior and inferior surgical care. NSQIP is an ongoing, prospective study involving 132 VA medical centers that gathers data on patient-specific factors affecting mortality and morbidity in the 30 days following major surgery. The study uses preoperative data to develop models of risk factors that predict surgical mortality and morbidity. The models can then be used to compute observed-to-expected mortality and morbidity ratios for each hospital, for surgical subspecialties, and for surgery as a whole. This unique program monitors the quality of VA's surgical care and provides important data for improving it.

Khuri SF, Daley J, Henderson W, et al. [The National VA Surgical Risk Study.] Risk Adjustment of the Post-operative Mortality Rate for the Comparative Assessment of the Quality of Surgical Care: Results of the National Veterans Affairs Surgical Risk Study. *Journal of the American College of Surgeons*, 185(4):315-327, 1997.

Chen AY, Daley J, Pappas TN, et al. Growing Use of Laparoscopic Cholecystectomy in the National Veterans Affairs Surgical Risk Study. *Annals of Surgery*, 227(1):12-24, 1998.

Longo WE, Virgo KS, Johnson FE, et al. Outcome After Proctectomy for Rectal Cancer in Department of Veterans Affairs Hospitals. A Report from the National Surgical Quality Improvement Program. *Annals of Surgery*, 228(1):64-70, 1998.

SDR #91-007, Hines

### **A VA study links smoking to abdominal aortic aneurysms.**

Abdominal aortic aneurysms kill 150,000 Americans each year. About 65 percent of patients die immediately when an aneurysm ruptures, and only half of those who make it to surgery survive. Because many people with aneurysms show no symptoms, it is critical to identify risk factors for developing aneurysms.

A major VA study shows that smokers are more than five times as likely as non-smokers to develop abdominal aortic aneurysms. This research clearly demonstrates the link between smoking and aneurysms and suggests that screening efforts for this disease target older male smokers. The findings also reinforce the importance of smoking cessation.

The study, conducted at 15 VA medical centers, involved ultrasound screening of 73,451 patients ages 50 to 79 with no history of abdominal aortic aneurysms. Subjects also completed a questionnaire designed to deter-

mine risk factors. Researchers found that veterans with a longer history of smoking were at greater risk for developing aneurysms, and veterans who quit smoking reduced their risk for aneurysm. Veterans with a family history of aneurysm were twice as likely to develop it themselves. Women, African Americans and diabetics were found to have lower risks for developing aneurysms.

*Lederle F, Johnson G, Wilson SE, et al. Prevalence and associations of abdominal aortic aneurysm detected through screening. Aneurysm Detection and Management (ADAM). Annals of Internal Medicine, 126(6):441-449, 1997. CSP #379, West Haven*

### **Evaluation of graft materials for blocked vessels may help prevent leg amputations.**

Many veterans suffer from blockages of leg arteries, a painful condition that can cause tissue death and lead to amputation. This study will determine whether Dacron, Teflon, umbilical vein or the patient's own vein is a more effective material for surgical grafts that bypass these blockages. Results will lead to more successful operations and fewer leg amputations.

*Comparative Efficacy of Vascular Bypass Materials in Lower Extremity Revascularization. CSP #141, Palo Alto*

### **Kidney Disease**

#### **Anti-anemia drug for dialysis patients may be administered subcutaneously at lower dosage.**

More than 90 percent of hemodialysis patients experience severe anemia. A new drug, recombinant human erythropoietin, is very effective at combating this anemia, but its cost is \$5,000 to \$10,000 per patient annually. A few small studies suggest that dosage of this drug may be reduced by 30 to 50 percent if given subcutaneously rather than intravenously, without sacrificing its beneficial effects. There was a concern that patient discomfort and inconvenience might be increased as a result. However, a randomized, multi-center trial by VA with 208 patients found that recombinant human erythropoietin can be administered just as effectively subcutaneously as intravenously, with a dosage reduction of 32 percent and no substantial increase in patient pain or discomfort. As much as \$450 million could be saved annually in the United States, if this drug were administered subcutaneously to all hemodialysis patients.

*Collaborator: AMGEN Pharmaceuticals*

*Kaufman JS, Reda DJ, Fye CL, et al. [The Department of Veterans Affairs Cooperative Study Group on Erythropoietin in Hemodialysis Patients.] Subcutaneous Compared With Intravenous Epoetin in Patients Receiving Hemodialysis. New England Journal of Medicine, 339(9):578-583, 1998. CSP #392, Hines*

### **Lung Disease**

#### **Shortened corticosteroid treatment for COPD is more cost-effective.**

VA research findings suggest modifying a common treatment for patients hospitalized with lung disease to improve cost-effectiveness and reduce patients' exposure to adverse side effects. Systemic corticosteroids have become a standard hospital therapy for patients with chronic obstructive pulmonary disease (COPD), despite known adverse effects and uncertain efficacy. VA researchers studied 271 patients to compare the safety and effectiveness of adding either systemic corticosteroids or placebo to other treatment. Results show that two weeks of corticosteroid therapy are as effective as eight weeks of therapy. Systemic corticosteroids improve lung function and shorten the average hospital stay by 1.2 days; however, they also cause hyperglycemia and other adverse effects.

*Niewoehner DE, Erbland ML, Deupree RH, et al. Effect of Systemic Glucocorticoids on Exacerbations of Chronic Obstructive Pulmonary Disease. New England Journal of Medicine. In Press, 1999. CSP#393, West Haven*

### **Seizures**

#### **Study demonstrates benefits of lorazepam in treating epileptic seizure.**

Epileptic seizure is a potentially fatal neurologic emergency that must be treated as quickly as possible to prevent death or severe, permanent brain damage. This CSP study compared four intravenous treatment regimens commonly used in the initial management of generalized epileptic seizure: phenytoin, diazepam plus phenytoin, phenobarbital, and lorazepam. The researchers found that although lorazepam was no more efficacious than the other treatments, it was easier to use and required less time to administer. Thus, use of lorazepam will allow emergency room staff more precious time to attend to these patients' urgent needs, resulting in better patient care.

*Collaborator: Parke-Davis; Wyeth-Ayerst Pharmaceuticals*  
*Treiman DM, Meyers PD, Walton NY, et al. [The Veterans Affairs Status Epilepticus Cooperative Study Group.] A Comparison of Four Treatments for Generalized Convulsive Status Epilepticus. New England Journal of Medicine, 339(12):792-798, 1998. CSP #265, Perry Point*

## **Low Back Pain**

### **Study evaluates the prognostic importance of MRI findings for low back pain.**

Low back pain is a frequent cause of disability and a common reason for outpatient care in veterans. Magnetic resonance imaging (MRI) of the lower back often reveals abnormalities, which may be used to justify expensive and invasive therapy, such as surgery. Yet the link between MRI abnormalities and the risk of developing clinically significant back pain is far from clear. This longitudinal study will determine the prevalence and incidence of MRI abnormalities among veterans and the extent to which specific MRI abnormalities predict future development of back pain. The results should help clinicians use MRI imaging more efficiently, and may ultimately reduce the frequency of unnecessary back surgery.

*A Prospective Cohort Study of MRI Imaging and Back Abnormalities.*  
EPP #97-014, Seattle

## ■ **Mental Illness**

### **Schizophrenia drug offers greater effectiveness, fewer side effects, and similar costs for refractory patients.**

Schizophrenia is chronic and the most disabling and costly of all mental illnesses. In VA, schizophrenia patients occupy 36% of all psychiatric inpatient beds. Standard antipsychotic medications do not alter the course of this disorder for many patients. A different drug, clozapine, shows great promise for alleviating symptoms of the disease in refractory patients, however, it is more costly and requires greater blood monitoring.

This completed study involving 15 VA medical centers and 423 patients, evaluated the cost-effectiveness of clozapine versus a standard antipsychotic drug, haloperidol. Results showed that clozapine was very effective in relieving the symptoms of disease, and in reducing hospital days thus offsetting the higher cost of the drug and blood monitoring. Results should inform practitioners and allow the drug to become more readily available to patients in need of it.

*Collaborator: Novartis Pharmaceuticals*

*Rosenheck R, Cramer J, XU W, et al. A Comparison of Clozapine and Haloperidol in Hospitalized Patients with Refractory Schizophrenia. The New England Journal of Medicine, 337(12):809-815, 1997.*  
CSP #17, Hines

### **Search for schizophrenia gene will improve treatment options.**

CSP researchers are hunting for the gene responsible for schizophrenia in a landmark study that will greatly expand understanding of the genetics of schizophrenia and hopefully result in the development of better treatments for this devastating disease. Investigators are combining their efforts with those of other researchers and collaborating with the private sector to ensure the study results in useful products.

*A Genetic Linkage of Schizophrenia.*  
CSP #366, Perry Point

### **Vitamin E holds promise for treating side effect in schizophrenia.**

Schizophrenia is a severe and chronic mental disorder that afflicts about 1 percent of all Americans and is commonly treated with anti-psychotic medications. These drugs may produce a severe side effect called "tardive dyskinesia" characterized by debilitating symptoms of involuntary, disfiguring facial movements. Up to now, this condition has been untreatable, but a new study by CSP will determine if a promising new vitamin E treatment can help. If the results are positive, this study will represent a long-awaited advance in the treatment of a catastrophic mental illness made even more unbearable by a medication that may cause a disfiguring side effect.

*Adler LA, Edson R, Lavori P, et al. Long-Term Treatment Effects of Vitamin E for Tardive Dyskinesia. Biological Psychiatry, 43(12):868-872, 1998.*  
CSP #394, Palo Alto

### **Manic-depression treatment aims to improve functional outcome and quality of life.**

Based on promising preliminary data, VA CSP will compare a high-intensity ambulatory treatment program for bipolar disorder against standard, office-based, physician-centered care. This devastating disorder affects many veterans and millions of Americans and their family members. The intervention seeks to improve manic and depressive symptom scores, as well as reduce total treatment costs compared to usual care of bipolar patients focusing on the particular issues of relapse-prevention that are critical for the VA.

*Reducing the Efficacy/Effectiveness Gap in Bipolar Disorder.*  
CSP #430, Palo Alto



### **Researchers look to group treatment model for relief of 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.

Group Treatment of PTSD.  
CSP #420, Palo Alto

### **Improved diagnostic tests sought for PTSD.**

Post-traumatic stress disorder (PTSD) is a serious health problem for many veterans, including those who served in Vietnam and the Persian Gulf. This study is developing psychological and physiological tests that can provide the means to accurately diagnose this condition and evaluate the progress of patients who are being treated.

Keane TM, Kolb LC, Kaloupek DG, et al. Utility of Psychophysiological Measurement in the Diagnosis of PTSD: Results from a Department of Veterans Affairs Cooperative Study. *Journal of Consulting and Clinical Psychology*, 66(6):914-923, 1998  
CSP #334, Palo Alto

### **Study addresses spread of infectious diseases in veterans with severe mental illness.**

In this CSP project, researchers are investigating the prevalence and spread of HIV and related infections, such as hepatitis C, among patients with severe mental illness. The goal is to identify risky behaviors that may aid the transmission of these diseases among these patients and the general population. Results of this study will help guide clinical management for these high-risk patients.

HIV Seroprevalence and Risks in Veterans with Severe Mental Illness.  
EPP #97-022, Durham

## **■ Aging and Age-Related Changes**

### **Outcomes of specialized care for elderly patients evaluated.**

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.

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

### **VA research shows effectiveness of cholesterol screening in the elderly.**

New research from VA supports cholesterol screening for the elderly, dispelling the controversy concerning the cost-effectiveness of cholesterol reduction in people over the age of 65 with no known heart disease. This study evaluated the role of guidelines for cholesterol screening among people over and under the age of 65 years. Preliminary results reveal that although total cholesterol is a poor predictor of coronary heart disease among people over 65, measures of LDL and HDL cholesterol are good predictors in both those older and younger than 65 years of age. These data, combined with recent randomized trial data, demonstrate the effectiveness of cholesterol screening of adults even older than 65 years.

Cholesterol Reduction in the Elderly.  
EPP #97-067, Seattle

### **Major trial launched to test new vaccine against shingles.**

Shingles in older people is extremely painful and can be disabling. 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 will test a promising new vaccine for its ability to prevent shingles or reduce its severity and

complications. The randomized, controlled trial will enroll 35,000 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.

*Collaborator: Merck Pharmaceuticals*

Trial of Varicella Vaccine for the Prevention of Herpes Zoster and its Complications.  
CSP #403, West Haven

### **Study compares drug treatments for elderly epilepsy patients.**

New-onset epilepsy occurs among 45,000 to 50,000 elderly people every year. These patients are especially vulnerable to side effects from drug treatments and often have other conditions for which they take medication. This study will compare the effects of two drugs recently approved for the treatment of seizures, gabapentin and lamotrigine, with a standard drug, carbamazepine, in elderly patients. Identification of a more effective drug for elderly people would allow these patients to live better, more seizure-free lives with fewer side effects.

*Collaborator: Glaxo-Wellcome; Parke-Davis Pharmaceuticals*

Treatment of Seizures in the Elderly Population.  
CSP #428, Perry Point

## **■ Health Services and Systems**

### **Intensive primary care for chronically ill did not improve post-discharge outcomes.**

Rapid access to high-quality primary care for patients discharged from the hospital with severe chronic illnesses greatly improves patient satisfaction with care but increases the likelihood of hospital readmission, this CSP study found. In a randomized, controlled trial at nine VA medical centers, 1,396 severely ill veterans with diabetes, chronic lung disease or congestive heart failure received either usual care or an intensive primary care intervention that involved close-follow-up by a nurse and primary care physician. Although they received more intensive primary care than the control group, patients in the intervention groups had significantly higher rates of readmission and more days of re-hospitalization. Patients receiving intensive primary

care were more satisfied with their care, but there was no difference between the study groups in quality-of-life scores, which remained very low.

*Weinberger M, Oddone EZ, Henderson WG, et al. Does increased access to primary care reduce hospital readmissions? New England Journal of Medicine, 334(22):1441-1447, 1996.  
CSP # 8, Hines*

### **Home-based primary care model goes under the microscope.**

This multi-site, randomized trial is evaluating the effectiveness of team-managed, home-based primary care (HBPC) in the VA system. Researchers are comparing this approach in terms of cost, satisfaction and patient outcomes with other types of post-acute care for veterans. Positive results could lead to the establishment of additional HBPC programs and expansion of existing programs, so that more patients may benefit from needed services.

*Hughes SL, Ulasevich A, Weaver FM, et al. Impact of home care on hospital days: a meta-analysis. Health Services Research, 32(4):415-432, 1997.  
CSP # 3, Hines*

### **VA takes steps to improve quality of informed consent.**

Informed consent is an issue of growing concern to researchers as they must ensure that patients participating in clinical trials are fully aware of what they are doing and the possible risks involved. VA's Informed Consent Quality Initiative will improve the methods used to inform patients about taking part in these studies and make sure that their consent is informed and voluntary. It will also provide an auditing method for certifying that the consent process used in VA studies meets VA's high standards.

*Lavori PW, Sugarman J, Hays MT, Feussner JR. Improving informed consent in clinical trials: a duty to experiment. Controlled Clinical Trials 1999. In Press.  
CSP #477, Palo Alto*

## **■ Military and Environmental Exposures**

### **VA tests antibiotic treatment for patients with Gulf War Illnesses.**

In this CSP study, VA researchers are testing a possible treatment for Gulf War Illnesses. Although the cause of GWI is unknown, one explanation that has received fairly wide attention holds that systemic Mycoplasma

fermentans infection may be responsible. The purpose of this recently approved 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 treatment could improve symptoms and possibly cure many veterans with GWI.

*Collaborator: Pfizer Pharmaceuticals*

Antibiotic Treatment of Gulf War Illnesses.

CSP #475, Perry Point

### **VA study assesses new approaches for treating veterans with Gulf War Illnesses.**

There is no definitive therapy for treating 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 also be used to help veterans with GWI. A cohort of 1356 GWI patients are being enrolled and randomized to one of four treatment groups: cognitive behavioral therapy plus aerobic exercise, aerobic exercise alone, cognitive behavioral therapy alone, and usual and customary care. Treatment will be provided for three months and patient outcomes will be tracked for a year. Hopefully, this research will provide needed answers for veterans who suffer from these mysterious and often disabling illnesses.

A Randomized, Multi-Center, Controlled Trial of Multi-Modal Therapy in Veterans with Gulf War Illness.

CSP #470, West Haven

### **VA survey assesses health of Persian Gulf War veterans and their families.**

A large-scale survey by VA of Persian Gulf War veterans and their families will help guide future policy regarding the appropriate care and support of these veterans, many of whom have complained of a variety of symptoms collectively known as Gulf War Syndrome. To date, researchers have surveyed veterans by mail and by telephone for this legislatively mandated study. In the study's current phase, researchers are conducting clinical examinations of a sample of 1,000 Gulf War

veterans and their spouses and children and 1,000 Gulf War-era veterans who were not deployed and their spouses and children. Sixteen VA medical centers are participating. So far, veterans and their families express a high level of satisfaction with their participation in the study.

National Health Survey of Gulf War Veterans and Their Families – Phase III Physical Examinations.

CSP #458, Hines

## **■ Sensory Loss**

### **Hearing aids compared in large-scale trial.**

More than 14 million Americans with hearing impairment could benefit from a hearing aid. However, there are few sound scientific data on the relative safety and efficacy of different types of hearing aids. This study will compare three types of hearing aids to determine which aids work best for certain patients. This unique trial will provide unbiased, scientific findings on hearing aids that could have a tremendous impact on quality of life for people with hearing impairment.

*Collaborator: National Institute on Deafness and other Communication Disorders (NIDCD)*

National Institute on Deafness and other Communication Disorders (NIDCD)/VA Hearing Aid Trial.

CSP #418, Hines

### **Multi-center trial looks at cataract complications.**

Cataract extraction is the most common surgical procedure in the US; about 1.2 million of these operations are performed annually. Vitreous loss, the most common complication of cataract surgery, occurs in about 1,000 VA patients every year. About one-third of these patients experience visual handicap for the rest of their lives. This multi-center trial will identify the most effective response to vitreous loss caused by cataract surgery. Improved vision for patients with this complication could save VA \$500,000 per year and have an enormous impact on cataract surgery outcomes.

Comparison of Anterior and Posterior Chamber Lens Implants After Vitreous Loss in Attempted Extracapsular Cataract Extraction.

CSP #338, Perry Point

## ■ Substance Abuse

### **Long-term use of naltrexone for alcoholism investigated.**

Alcoholism is a tenacious, chronic illness with devastating physical and mental health consequences.

Naltrexone is the most promising new medication in the search for an effective treatment for alcoholism.

Although naltrexone was approved for short-term use by the Food and Drug Administration, knowledge about the long-term use of this treatment is limited.

This major, multi-hospital trial will evaluate the efficacy, effectiveness and durability of naltrexone in the treatment of alcohol-dependent veterans. The study results may have an enormous impact on the health of alcohol-dependent veterans and others, and on the significant health care costs associated with alcoholism.

*Collaborator: DuPont Pharmaceuticals*

Naltrexone in the Treatment of Alcoholism.

CSP #425, Perry Point

### **Lecithin may hold key to preventing cirrhosis.**

Cirrhosis of the liver is a leading cause of death in the US. Currently, there is no way to prevent or cure it.

However, highly successful animal studies suggest that a vitamin called lecithin may act as a preventive agent against cirrhosis. This CSP study will test that observation further. If lecithin is found to be effective against cirrhosis, it will be the first treatment ever to provide an effective but simple approach to preventing cirrhosis. The impact on suffering, death and associated health care costs would be enormous.

*Collaborator: Rhone-Poulenc Rorer Pharmaceuticals*

Effect of Polyunsaturated Lecithin on Liver Fibrosis.

CSP #391, Perry Point

### **Colchicine may provide first effective treatment of cirrhosis.**

This study will serve as the definitive test of colchicine, a drug for the treatment of alcoholic cirrhosis of the liver, a highly fatal condition for which abstinence and proper nutrition are the only known treatments. Because alcoholic cirrhosis is a disabling disease with high rates of morbidity and mortality, identification of an effective treatment will have a significant impact on both quality of life and health care costs.

*Colchicine in the Treatment of Alcoholic Cirrhosis of the Liver:*

CSP #352, Perry Point

### **Sclerotherapy shows promise for treating esophageal varices.**

Alcoholics who have liver disease may develop veins in the throat called esophageal varices, which can burst, leading to hospitalization and death. The use of sclerotherapy in treating alcoholic patients with bleeding esophageal veins reduced the need for in-hospital medical care. This treatment enhanced efforts to stop bleeding, reduced the number of blood transfusions and hours required in intensive care, and improved in-patient survival. However, post-discharge longevity was not increased.

*Hartigan PM, Gebhard RL, Gregory PB. [The Veterans Affairs Sclerotherapy Group.] Sclerotherapy for actively bleeding esophageal varices in male alcoholics with cirrhosis. Gastrointestinal Endoscopy, 46(1):1-7, 1997.*

CSP #237, West Haven

### **NIDA taps CSP for help in combating cocaine addiction.**

Mounting a medical response to the national epidemic of cocaine abuse, the National Institute on Drug Abuse (NIDA) has enlisted CSP's help to produce a statistical infrastructure that will support rapid development of new drug abuse treatments. CSP's unique clinical and scientific resources will help NIDA evaluate treatment compounds more efficiently. The goal is to produce new treatment options and renew hope of reversing this scourge.

*Collaborator: National Institute on Drug Abuse (NIDA)*

Rapid Evaluation of Cocaine Pharmacotherapies: Amantadine.

A Multicenter Efficacy/Safety Trial of Buprenorphine/Naloxone for the Treatment of Opiate Dependence.

CSP #1010 and 1008, Perry Point

### **Combination drug treatment for opiate abuse under examination.**

Opiate abuse is a major health service issue in VA and in the country. VA researchers, with funding from the National Institute on Drug Abuse, are investigating the efficacy and safety of a combined buprenorphine and naloxone product that could expand treatment options for opiate dependence. If approved by the Food and Drug Administration, this tablet product could be dispensed at general health care clinics, rather than special substance abuse clinics, for patients to take home. This may increase treatment among patients who are negative for HIV and hepatitis.

*Collaborator: National Institute on Drug Abuse (NIDA);*

*Reckitt and Colman Pharmaceuticals*

Buprenorphine/Naloxone for Treatment of Opiate Dependence.

CSP #1008, Perry Point