VA RESEARCH & DEVELOPMENT
IMPACTS

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Paul M. Hoffman, M.D.
Director, Medical Research Service

Message from the Director

The VA Medical Research Service has played a major role in the Office of Research and Development's history of serving veterans and the United States as a whole. Its achievements in basic and clinical research frequently lay the groundwork for improved patient care.

For example, Ferid Murad, M.D., Ph.D., shared the 1998 Nobel Prize in Medicine in part for research he conducted while at the Palo Alto VA Medical Center. Studies by Dr. Murad, now at the University of Texas Medical School in Houston, have been instrumental in illuminating the role of nitric oxide in body functions including the relaxing of blood vessels and regulation of blood pressure. Additionally, the Nobel Prize for Medicine was shared in 1977 by two VA scientists, Rosalyn Yalow, Ph.D., of the Bronx VA Medical Center, and Andrew Schally, Ph.D., of the New Orleans VA Medical Center, both still active VA investigators. Dr. Yalow's work with radioisotopes formed the basis for modern routine diagnostic assays that use radioactive materials, and Dr. Schally was honored for key discoveries on the workings of the endocrine system.

Contributions of VA Medical Research also include many other landmark advances, including successful treatment for tuberculosis, the first successful liver and kidney transplants, the concept that led to development of the CAT scan, drugs for treatment of mental illness, and development of the cardiac pacemaker. The VA biomedical researchers of today continue this tradition of accomplishment. Among the latest notable advances are identification of genes linked to Alzheimer's disease and schizophrenia, new treatment targets and strategies for substance abuse and chronic pain, and potential genetic therapy for heart disease.

The Office of Research and Development and the Medical Research Service are proud of the role research plays in improving health care for veterans and advancing medical science worldwide. Following are highlights of some recent accomplishments by our investigators, including work by recipients of the William S. Middleton Award, the Medical Research Service's highest scientific honor. Each highlight is followed by a citation, the principal investigator's name, location and funding source.

Paul M. Hoffman, M.D.
Director

Neurotrauma and Neurodegenerative Disease

Early treatment with corticosteroids reduces damage from SCI.

More than 1 million Americans live with disabilities resulting from spinal cord injuries. 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.

Anderson DK, Hall ED. Pathophysiology of spinal cord trauma. Annals of Emergency Medicine 1993;22(6):987:92.
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 1997;148(2):523-43.
Douglas K. Anderson, Ph.D., VAMC Gainesville, FL
VA Merit Review, Medical Research Service

VA researchers make breakthrough in brain tumor treatment.

Researchers at the Portland VAMC have paved the way for brain tumor treatment with powerful drugs by pioneering methods that allow these drugs to cross what is known as the "blood-brain barrier." In addition, they have designed an intervention to prevent or reduce hearing loss, a serious side effect of this new treatment in many brain tumor patients.

The blood-brain barrier serves as a wall protecting brain tissue, but it also prevents large-molecule chemotherapy drugs such as carboplatin from reaching tumors inside the brain. Using a sugar solution to temporarily shrink barrier cells and create spaces between them, VA researchers opened the gate for drugs such as carboplatin to treat tumors. They subsequently found that carboplatin was one of the most effective therapies for brain tumors.

However, carboplatin unexpectedly caused major hearing loss in many brain tumor patients, who needed hearing aids following therapy. VA investigators devised a two-stage treatment approach, using sodium thiosulfate (STS) to prevent hearing loss after administering carboplatin therapy. Results were highly encouraging. STS apparently protects hearing by binding to the platinum in carboplatin before it can harm the inner ear. The VA team's work with STS may also prove useful in combating hearing loss associated with platinum-based chemotherapy treatment of other types of cancer, such as cancer of the ovary and lung.

Kroll RA, Neuwelt EA. Outwitting the blood-brain barrier for therapeutic purposes: osmotic opening and other means. Neurosurgery 1998;42(5):1083-99.
Neuwelt EA, Brummett RE, Doolittle ND, Muldoon LL, Kroll RA, Pagel MA, Dojan R, Church V, Remsen LG, Bubalo JS. First evidence of otoprotection against carboplatin-induced hearing loss with a two-compartment system in patients with central nervous system malignancy using sodium thiosulfate. Journal of Pharmacology and Experimental Therapeutics 1998;286(1):77-84.
Edward A. Neuwelt, M.D., Portland VA Medical Center
VA Merit Review, Medical Research Service

New approach against chronic pain holds promise.

Chronic pain can be debilitating, and effective treatment hinges on the ability to find mechanisms that distinguish persistent and pathological pain from normal pain sensations that protect us from injuries and burns. Working together, two VA researchers have identified a possible treatment for chronic pain that combines a toxin called saporin and substance P, a peptide naturally released in the spinal cord in response to pain. When the researchers infused the spinal fluid of laboratory rats with a substance P-toxin complex, their responsiveness to mild stimuli, such as touch or warm heat, remained normal. But when the animals received a much stronger stimulus in the form of an irritant to the pads of their feet, the infusion of substance P appeared to prevent hypersensitivity to the pain that normally would be caused by this irritant.

These results suggest that substance P receptors are crucial in the hypersensitivity found in chronic pain

and they might be destroyed by infusing them with a substance P-toxin complex. Research is continuing to determine the utility of substance P for chronic pain treatment.

Mantyh PW, Rogers SD, Honore P, Allen BJ, Ghilardi JR, Li J, Daughters RS, Lappi DA, Wiley RG, Simone DA. Inhibition of hyperalgesia by ablation of lamina I spinal neurons expressing the substance P receptor. Science 1997;278(5336):275-9.

Patrick W. Mantyh, Ph.D., VAMC Minneapolis, MN
Ronald G. Wiley, M.D., Ph.D., VAMC Nashville, TN
VA Merit Review, Medical Research Service

New research finding may lead to treatment for tinnitus.

At some time in their lives, as many as 35 percent of all Americans suffer from tinnitus, a disabling ringing in the ears that impairs hearing. About 10 percent of elderly Americans have severe tinnitus, which may lead to depression, anxiety, insomnia and other problems. Treatment of this mysterious condition has been difficult without information on how and where it originates. In a finding that may lead to an eventual cure, a team of VA researchers reports that they have located the brain region responsible for tinnitus.

Although most people with tinnitus have no control over the ringing, a few can vary the volume of the ringing by moving their jaws. VA researchers used positron emission tomography (PET) scanning to study a small number of these patients while they clenched and unclenched their jaws, tracking blood flow in different parts of the brain when the ringing was loud or soft. The researchers then tracked the source of the noise to the auditory cortex, a part of the brain in the temporal lobe opposite the affected ear. Scans also revealed that tinnitus activates the limbic system, a brain region associated with emotion. This finding may explain why people with severe tinnitus are prone to depression and other emotional problems.

Much work remains to identify factors that cause tinnitus-related brain changes. However, now that they know where tinnitus originates, the researchers may be able to develop new drugs that alter the activity of brain chemicals in affected areas and turn off the phantom ringing.

Lockwood AH, Salvi RJ, Coad ML, Towsley ML, Wack DS, Murphy BW. The functional neuroanatomy of tinnitus: evidence for limbic system links and neural plasticity. Neurology 1998;50(1):114-20.

Alan H. Lockwood, M.D., Buffalo VA` Medical Center
National Institute on Deafness and Other Communication 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's studies 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.

Knowlton BJ, Mangels JA, Squire LR. A neostriatal habit learning system in humans. Science 1996;273(5280):1399-1402.

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

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

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

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 some 4 million elderly 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.

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 1996;272(5259):258-62.
Payami H, Schellenberg GD, Zareparsi S, Kaye J, Sexton GJ, Head MA, Matsuyama SS, Jarvik LF, Miller B, McManus DQ, Bird TD, Katzman R, Heston L, Norman D, Small GW. Evidence for association of HLA-A2 allele with onset age of Alzheimer's disease. Neurology 1997;49(2):512-18.
Poorkaj P, Bird TD, Wijsman E, Nemens E, Garruto RM, Anderson L, Andreadis A, Wiederholt WC, Raskind M, Schellenberg GD. Tau is a candidate gene for chromosome 17 frontotemporal dementia. Annals of Neurology 1998;43(6):815-25.
Gerard Schellenberg, Ph.D., VA Puget Sound Health Care System
VA Merit Review, Medical Research Service

Research efforts target animal models for studying Alzheimer's Disease.

Dementia and memory loss are among the most visibly disturbing aspects of Alzheimer's disease. Dementia, caused by the death of cells in various parts of the brain, typically progresses as the brain shows distinct atrophy, marked by the presence of senile plaques and neurofibrillary tangles.

Research by VA offers the possibility of the first useful animal models for studying Alzheimer's, which has been an exclusively human disorder. VA researchers are studying whether high levels of human proteins believed to be involved in the development of Alzheimer's produce Alzheimer-like lesions in transgenic mice. They have also identified nearly all types of Alzheimer-like lesions in aged sheep. Another line of investigation is focusing on whether lesions target specific parts of the brain's cortex. Findings from these studies will lead to greater understanding of how Alzheimer's develops, as well as new strategies for treatment and prevention.

Kuljis RO, Xu Y, Aguila MC, Baltimore D. Degeneration of neurons, synapses, and neuropil and glial activation in a murine ATM knockout model of ataxia-telangiectasia. Proceedings of the National Academy of Sciences USA 1997;94(23):12688-93.
Rodrigo O. Kuljis, M.D., VAMC Miami, FL
VA Merit Review, Medical Research Service

■ Mental Health and Addiction

VA researchers discover schizophrenia-associated gene.

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, VA researchers 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 then 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. This suggests that schizophrenia may represent a disorder of sensory processing known as "gating."

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. VA researchers are investigating the cause of the genetic malfunction and are collaborating with drug companies to identify potential drugs to bind the receptors.

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 1997;94(2):587-92.

Robert Freedman, M.D., VAMC Denver, CO
Special Research Initiatives

VA investigator finds important link between youthful drinking and later alcoholism.

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 — clearly raising 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.

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

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

Alcohol damages memory and learning systems in the young, research shows.

Through a series of animal studies, VA researchers have made the important discovery that young people are more susceptible than adults are to alcohol-induced learning and memory problems. Because alcohol disrupts nerve function more in young people than in mature people, young people become more tolerant more quickly to the effects of alcohol, the researchers found. They are also more prone to develop memory-related difficulties as a result of alcohol consumption.

Young people are less likely to become sleepy after consuming alcohol, and thus more likely to stay awake for longer periods, during which they may consume more alcohol and increase their risk of memory and learning damage. As few as two drinks can inhibit learning and memory in a young person while having little effect on an adult. These results hold significant implications for public education efforts aimed at minors and young adults.

Little PJ, Kuhn CM, Wilson WA, Swartzwelder HS. Differential effects of ethanol in adolescent and adult rats. Alcoholism: Clinical & Experimental Research 1996;20(8):1346-51.

Harry Scott Swartzwelder, Ph.D., VAMC Durham, NC
Alcoholic Beverage Medical Research Foundation

Researchers identify brain peptides as potential substance abuse therapy.

The devastating effects of substance abuse remain a serious problem for the veteran population. More than 25 percent of veterans treated at VA medical facilities suffer from some form of substance abuse.

VA researchers have discovered that two brain peptides can help treat addictive disorders and relieve pain. They found that the two peptides, both endorphins, bind to the part of brain affected by morphine-related analgesics and abusive drugs, acting as powerful pain relievers.

Peptides are natural brain products and therefore less likely to cause adverse side effects than other pharmacological therapies. Because endorphins affect cardiovascular, digestive, endocrine, and immune system functions as well as pain, this discovery may have far-reaching applications for a variety of health problems.

Zadina JE, Hackler L, Ge LJ, Kastin AJ. A potent and selective endogenous agonist for the mu-opiate receptor. Nature 1997;386(6624):499-502.

James E. Zadina, Ph.D., VAMC New Orleans, LA
VA Merit Review, Medical Research Service

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.

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

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

Cardiovascular, Renal, and Endocrine Disorders

VA researcher explores role of renal nerves in kidney function.

Gerald F. DiBona, M.D., who won the 1995 Middleton Award for his internationally recognized research in renal and cardiovascular diseases, has made major breakthroughs in understanding the role of renal nerves in regulating kidney function. His work in advancing the knowledge of disorders marked by excess water and sodium retention may point the way to new treatments targeting errors in metabolic pathways.

Dr. DiBona and his colleagues have provided evidence that abnormal renal nerve activity disrupts the kidney's ability to filter impurities, regulate blood flow, and control the vital balance of sodium and water excretion. These failures cause the sodium and water retention that contributes to conditions such as hypertension, cirrhosis, and heart failure. They have also identified the mechanisms by which renal nerves influence sodium retention, including the interaction

between renal nerves and sodium-retaining systems.

Dr. DiBona's research team is now pursuing an investigation into how the renal nerves and sodium-retaining systems augment each other's effects. In another project, the researchers are finding that mice with abnormalities in renal nerve function go on to develop a genetic form of salt-dependent high blood pressure.

DiBona GF, Jones SY. Reflex effects on components of synchronized renal sympathetic nerve activity. American Journal of Physiology 1998;275(3 Pt 2):F441-6.

Gerald F. DiBona, M.D., Iowa City VA Medical Center
VA Merit Review, Medical Research Service

VA investigator makes important advances in diabetes and insulin research.

Daniel Porte, Jr., M.D., winner of the 1996 Middleton Award, has laid the foundation for current understanding of pancreatic malfunctions that trigger type 2 or non-insulin dependent diabetes. This form of diabetes, in which the body secretes insufficient and ineffective insulin, usually develops in adults over age 40, including many aging veterans.

Dr. Porte and his colleagues are especially well known for their studies on the role of pancreatic beta cells. They defined the separate but interactive roles of insulin secretion, insulin sensitivity, and glucose effectiveness — all abnormal in people with type 2 diabetes — in controlling glucose tolerance. Dr. Porte's team is also evaluating several new drugs for diabetes treatment.

In addition to his diabetes studies, Dr. Porte has made important discoveries regarding the effects of insulin and other hormones on body weight. For example, he was the first to propose — and demonstrate — that insulin regulates body weight by acting on the brain. This research has enormous potential importance for the millions of Americans who are seriously overweight and at higher risk to develop disorders such as diabetes, coronary artery disease, and hypertension.

Kahn SE, Prigeon RL, McCulloch DK, Boyko EJ, Bergman RN, Schwartz MW, Neifing JL, Ward WK, Beard JC, Palmer JP, Porte D Jr, et al. Quantification of the relationship between insulin sensitivity and beta-cell function in human subjects. Evidence for hyperbolic function. Diabetes 1993;42(11):1663-72.

Woods SC, Seeley RJ, Porte D Jr, Schwartz MW. Signals that regulate food intake and energy homeostasis. Science 1998;280(5368):1378-1383.

Daniel Porte, Jr., M.D., VA Puget Sound Health Care System
VA Merit Review, Medical Research Service

Gene therapy shows promising results for heart disease.

VA investigators are at the cutting edge of research into gene therapy to treat heart failure, hypertension, and the clogged arteries of atherosclerosis.

For example, in a recent VA study, researchers found that inserting a certain gene into heart cells triggered a robust increase in the chemical that drives the cells to beat more strongly. This approach ultimately may be used to help people with congestive heart failure, reducing their symptoms and prolonging their lives.

The researchers started by focusing on ways to enhance the signaling system that normally tells the heart muscle to contract more strongly when more blood is needed. In patients with congestive heart failure, the heart fails to respond to these signals. This disorder often causes severe disability and early death, and current treatments frequently are ineffective.

The researchers concentrated their efforts on a fight-or-flight enzyme called adenylate cyclase, which produces cAMP, the substance that commands an increase in heart function. After infusing heart muscle cells in laboratory dishes with adenylate cyclase, cAMP production increased by six or seven times, with no negative effects on the cells. The researchers are now completing animal studies using this approach.

VA researchers also reported successful gene therapy in animals to increase the numbers of blood vessels that carry oxygen to the heart muscle. Clinical trials will soon begin to evaluate this treatment in patients with ischemia, reduced blood flow and oxygen that can lead to heart attacks.

Gao M, Ping P, Post S, Insel PA, Tang R, Hammond HK. Increased expression of adenylylcyclase type VI proportionately increases beta-adrenergic receptor-stimulated production of cAMP in neonatal rat cardiac myocytes. Proceedings of the National Academy of Sciences, USA 1998;95(3):1038-43.

Giordano FJ, Ping P, McKirnan MD, Nozaki S, DeMaria AN, Dillmann WH, Mathieu-Costello O, Hammond HK. Intracoronary gene transfer of fibroblast growth factor-5 increases blood flow and contractile function in an ischemic region of the heart. Nature Medicine 1996;2(5):534-9.

Kirk Hammond, M.D., VA San Diego Health Care System
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