

NAVAL HEALTH RESEARCH CENTER

SEEKING TREATMENTS FOR GULF WAR VETERANS' ILLNESSES

*J. McKeehan
S. Clark
M. Ryan*

20040329 016

Report No. 01-19

Approved for public release; distribution unlimited.

NAVAL HEALTH RESEARCH CENTER
P. O. BOX 85122
SAN DIEGO, CA 92186-5122



BUREAU OF MEDICINE AND SURGERY (MED-02)
2300 E ST. NW
WASHINGTON, DC 20372-5300



Seeking Treatments for Gulf War Veterans' Illnesses

Jamie McKeehan, BS
Suzanne Clark, BA
LCDR Margaret Ryan, MC, USN

Gulf War veterans in the San Diego area were recently given an important opportunity to help researchers learn how to treat chronic multi-symptom illnesses. The Department of Defense (DOD) Center for Deployment Health Research at the Naval Health Research Center, San Diego, is participating in two large clinical trials to treat nonspecific illnesses among Gulf War veterans. One of more than 30 sites nationwide, the Naval Health Research Center is the only Navy site involved in these Department of Veterans Affairs (VA)-DOD cooperative studies. Other sites include the Walter Reed Army Medical Center, Washington, DC, and 28 VA medical centers across the country.

What Is "Gulf War Illness?"

Nearly 700,000 U.S. service members deployed to the Persian Gulf region for Operations Desert Shield and Desert Storm in 1990-91.

Although the conflict was brief and extraordinarily successful for the U.S. and allied forces, our troops were still exposed to the hazards of war and the environment.

Concerning exposures included sand, insects, temperature fluctuations, jet fuel, smoke from burning oil wells, chemical munitions, medical chemoprophylactic agents, vaccines, insect repellants, and the general stressors of war.(1)

In the years following the Gulf War, many service members reported health concerns. Although the appearance of post-deployment medical problems was not unique to this conflict,(2) registries were developed to chronicle the veterans' concerns,(3) and tremendous resources have been spent to investigate the nature and causes of Gulf War veterans' health problems. A recent bibliography comprises more than 5,000 articles published on Gulf War health issues,(4) and details almost \$150 million spent on research.

The results of epidemiological research have been reassuring for an absence of severe morbidity associated with Gulf War deployment. Compared with their non-deployed colleagues, veterans of the conflict appear no more likely to have experienced hospitalizations, cancer, children with birth defects, or mortality.(5-10) Ongoing



Photos by Robb Reed, Naval Health Research Center

Current staff of the Clinical Trials Center in San Diego includes (back, left to right) Jamie McKeehan, LCDR Margaret Ryan, LCDR Julie Stenger; (front, left to right) Dr. Bill Matulich, Debbie Kamens, Deena Friedlander, and Esther Hudson.

research continues to explore these important health outcomes.

In contrast to severe problems, Gulf War veterans have reported more ill-defined, symptom-based conditions than their non-deployed peers.⁽¹¹⁻¹⁴⁾ Chronic fatigue, chronic pain, memory and concentration problems in the absence of other known medical conditions have been especially frustrating for some Gulf War veterans. With causes of their symptoms still unknown almost 10 years after deployment, many veterans have sought relief from unproven remedies. VA and DOD investigators, recognizing the needs of these veterans, are now exploring ways to help treat the chronic, multi-symptom disorders that are sometimes called Gulf War illnesses.

VA-DOD Cooperative Study # 470: Exercise and Cognitive Behavioral Therapy Trial

Chronic multi-symptom conditions have long been experienced by the general population, causing similar di-

agnostic frustration in the medical community. In recent years, such symptom conditions have been given various names, including chronic fatigue syndrome, irritable bowel syndrome, multiple chemical sensitivities, fibromyalgia, and post traumatic stress disorder. While the nature and diagnostic criteria for these conditions are not always agreed upon, some empirical treatments have proved promising in relieving the suffering of those affected.

Cognitive behavioral therapy (CBT) is one such treatment. The theory behind CBT recognizes the experience of pain as a complex integration of pathophysiology, cognition, affect, and behavior. Relaxation training, activity pacing, pleasant activity scheduling, goal setting, and visual imagery techniques are skills commonly associated with CBT treatments for chronic pain. Several randomized, controlled trials have suggested that CBT is effective in the management of fibromyalgia and chronic fatigue syndrome, as well as the better-defined disorders of rheumatoid arthritis, multiple sclerosis, and coronary artery disease.⁽¹⁵⁻¹⁷⁾

Another type of therapy that seems to be effective for treating a wide range of chronic illness is aerobic exercise. Many studies indicate that involvement in an aerobic exercise program can improve cardiovascular fitness as well as symptoms associated with fibromyalgia, chronic fatigue syndrome, rheumatoid arthritis, and mood disorders.^(18, 19) Researchers have found that adherence to a lifelong program of exercise that gradually increases in intensity is most effective.⁽²⁰⁾

The goal of VA-DOD Cooperative Study #470 is to assess the value of exercise and cognitive behavioral therapy in Gulf War veterans who have experienced at least two of the following three symptoms: (1) fatigue that limits their usual activities, (2) pain in at least two regions of the body, and (3) problems with memory or concentration. Volunteers with these symptoms were randomized to receive either CBT, exercise therapy, both, or usual care. They have been followed with assessments of their symptoms, general functioning, pain tolerance, and exercise tolerance over the course of 1 year.

Nationally, nearly 1,100 veterans are participating in this study. The San Diego site has contributed an important part of this number. Naval Health Research Center professionals involved in the exercise and cognitive behavioral therapy study include Esther Hudson, study coordinator; Dr. Bill Matulich, clinical psychologist; Deena Friedlander, exercise physiologist; Jamie McKeehan and Lesley Henry, research assistants; and LCDR Julie

Stenger, LCDR Margaret Ryan, and CAPT Greg Gray, physician investigators. The study began enrollment in the summer of 1999 and will conclude in late 2001.

VA-DOD Cooperative Study # 475: Antibiotic Treatment Trial

One of the most interesting theories about chronic multi-symptom illnesses is that infections might play a role in their development. Some civilian researchers in California have popularized the theory that occult *Mycoplasma fermentans* infection causes chronic fatigue syndrome in Gulf War veterans and civilians alike.^(21,22) In the absence of rigorous clinical trials, Internet-driven marketing of this idea has drawn thousands of fatigue sufferers to seek long-term antibiotic treatment.

Recognizing that more extensive research was necessary before antibiotic treatment could be recommended for symptomatic veterans, the VA and DOD developed Cooperative Study #475. Patient-volunteers for this study are similar to those participating in Study #470 in that they are Gulf War veterans suffering from chronic fatigue, chronic pain, and/or memory and concentration problems. However, those participating in Study #475 have met the additional criterion of having a blood test showing evidence of mycoplasma infection. Blood drawn at local study sites was sent to a central laboratory for mycoplasma testing; a very sensitive molecular detection method was used that is not available in most clinical laboratories.

Patient-volunteers who tested positive for mycoplasma infection agreed to be randomized to treatment with either an antibiotic (doxycycline) or placebo (inactive pill) for the next 12 months. Follow-up visits were required monthly throughout the year, and again 6 months after the treatment trial was complete. Participants were assessed for their symptoms, general functioning, and blood test results at regular intervals.

Nationwide, 491 veterans were randomized in this study, and many were from the San Diego area. Naval Health Research Center professionals involved in the antibiotic treatment trial include Debbie Kamens, study coordinator; Jamie McKeehan, research assistant; and LCDR Stenger, LCDR Ryan, and CAPT Gray, physician investigators.

Results of the Treatment Trials

Both treatment trials began in the summer of 1999 and are ongoing. The strict research protocols require that investigators are "blinded" to results before the nation-

wide efforts are complete, so it is still too early to know exactly how well the treatments may have worked.

Even at this stage, however, some information from the Naval Health Research Center is extremely positive. The team in San Diego, led by CAPT Gray, has worked hard to recruit all interested Gulf War veterans, and these efforts have been very well received. Coverage from the local television and newspapers in San Diego has prompted praise for the team's caring efforts. Quotes from patient-volunteers include: "The staff is probably the most professional medical staff I have encountered ... they genuinely care about all aspects of treatment ... it is a pleasure to be in this program!" and "Extremely customer oriented ... I was treated like royalty, efficiently, expeditiously, and courteously." Further validating this work, rigorous VA audits revealed that San Diego was a top-performing site for best clinical research practices.



Deena Friedlander, exercise physiologist, displays some of the equipment used by patient-volunteers at the Clinical Trials Center.

Although it may be some time before the research results are fully available, the team at the Naval Health Research Center will continue to provide quality investigative care for all service members. The researchers in San Diego are quick to credit their patient-volunteers for the commitment and sacrifice that make clinical research possible. The efforts of these veterans are likely to benefit not only their fellow service members, but all people with chronic multi-symptom illnesses.

VA-DOD Cooperative Study Information

VA-DOD Cooperative Studies #470 and #475 are led nationally by Dr. John Feussner, Chief Research and Development Officer, Department of Veteran Affairs; Dr. Sam Donta, Professor of Medicine, Boston VA Medical Center; COL Charles Engel, MC, USA, of Walter Reed Army Medical Center, Washington, DC, and Dr. Daniel Clauw, Professor of Medicine, Georgetown Medical Center, Washington, DC.

For more information on research performed by the DOD Center for Deployment Health Research at the Naval Health Research Center, visit <http://www.nhrc.navy.mil/rsch/code25/program5.htm>

References

1. Kroenke K, Koslowe P, Roy M. Symptoms in 18,495 Persian Gulf War veterans. *J Occup Environ Med.* 1998;40:520-528.
2. Hyams K, Wignall F, Roswell R. War syndromes and their evaluation: from the U.S. Civil War to the Persian Gulf War. *Ann Intern Med.* 1996;125:398-405.
3. Joseph S. The Comprehensive Clinical Evaluation Program Evaluation Team. A comprehensive clinical evaluation of 20,000 Persian Gulf War veterans. *Mil Med.* 1997;162:149-155.
4. Henry L, Gray G. *Topical Bibliography of Published Works Regarding the Health of Veterans of the Persian Gulf War.* San Diego, CA: Naval Health Research Center; 1999. Technical Document 99-3C (revised January 2001).
5. Gray GC, Coate BD, Anderson CM., et al. The postwar hospitalization experience of U.S. Persian Gulf War Veterans. *N Engl J Med.* 1996;335:1505-1513.
6. Gray G, Smith T, Knoke J, Heller J. The postwar hospitalization experience of Gulf War veterans possibly exposed to chemical munitions destruction at Khamisiyah, Iraq. *Am J Epidemiol.* 1999;150:532-540.
7. Knoke J, Gray G, Garland F. Testicular cancer and Persian Gulf War service. *Epidemiology* 1998;9:648-653.
8. Cowan D, DeFraitres R, Gray G, Goldenbaum M, Wishik S. The risk of birth defects among children of Persian Gulf War veterans. *N Engl J Med.* 1997;336:1650-1656.
9. Writer J, DeFraitres R, Brundage J. Comparative mortality among U.S. military personnel in the Persian Gulf region and worldwide during Operations Desert Shield and Desert Storm. *JAMA.* 1996;275:118-121.
10. Kang H, Bullman T. Mortality among U.S. veterans of the Persian Gulf War. *N Engl J Med.* 1996;355:1498-1504.
11. Gray GC, Kaiser KS, Hawksworth AW, Hall FW, Barrett-Connor EL. Increased postwar symptoms and psychological morbidity among U.S. Navy Gulf War veterans. *Amer J Trop Med Hyg.* 1999;60:758-766.
12. Coker WJ, Bhatt BM, Blatchley NF, Graham JT. Clinical findings for the first 1000 Gulf War veterans in the Ministry of Defence's medical assessment programme. *BMJ.* 1999;318:290-294.
13. Fukuda K, Nisenbaum R, Stewart G, et al. Chronic multisymptom illness affecting Air Force veterans of the Gulf War. *JAMA.* 1998;280:981-988.
14. The Iowa Persian Gulf Study Group. Self-reported illness and health status among Persian Gulf War veterans: a population-based study. *JAMA.* 1997;277:238-245.
15. Deale A, Chalder T, Marks I, Wessely S. Cognitive behavioral therapy for chronic fatigue syndrome: a randomized controlled trial. *Am J Psychiatry.* 1997;154:408-414.
16. Gruber A, Hudson J, Pope H, Jr. The management of treatment-resistant depression in disorders on the interface of psychiatry and medicine. Fibromyalgia, chronic fatigue syndrome, migraine, irritable bowel syndrome, atypical facial pain, and premenstrual dysphoric disorder. *Psychiatr Clin North Am.* 1996;19:351-369.
17. Bradley L. Cognitive-behavioral therapy for primary fibromyalgia. *J Rheumatol Suppl.* 1989;19:131-136.
18. Janal M. Pain sensitivity, exercise and stoicism. *J R Soc Med.* 1996;89:376-381.
19. Martin L, Nutting A, MacIntosh B, Edworthy S, Butterwick D, Cook J. An exercise program in the treatment of fibromyalgia. *J Rheumatol.* 1996;13:1050-1053.
20. Clark SR. Prescribing exercise for fibromyalgia patients. *Arthritis Care Res.* 1994;7:221-225.
21. Nicolson G, Nicolson N. Diagnosis and treatment of mycoplasma infections in Persian Gulf War illnesses-CFIDS patient. *Int J Occup Med Tox.* 1996;5:69-78.
22. Nicolson G, Nicolson N. Chronic fatigue illness and Operation Desert Storm. *J Occup Environ Med.* 1996;38:14-16. □

Dr. Margaret Ryan is the Director of the DOD Center for Deployment Health Research at the Naval Health Research Center in San Diego.

Jamie McKeehan and Suzanne Clark are members of the research staff at the DOD Center for Deployment Health Research.

REPORT DOCUMENTATION PAGE

The public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing the burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB Control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.

1. Report Date (DD MM YY) Apr 2000	2. Report Type Final	3. DATES COVERED (from - to) Jun 99 to Oct 01
4. TITLE AND SUBTITLE Seeking Treatments for Gulf War Veterans' Illnesses		5a. Contract Number:
6. AUTHORS Jamie A. McKeehan, Suzanne Clark, Margaret AK RyanI		5b. Grant Number:
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Naval Health Research Center P.O. Box 85122 San Diego, CA 92186-5122		5c. Program Element:
8. SPONSORING/MONITORING AGENCY NAMES(S) AND ADDRESS(ES) Chief, Bureau of Medicine and Surgery Code M2 2300 E St NW Washington DC 20372-5300		5d. Project Number: Reimbursable
		5e. Task Number:
		5f. Work Unit Number: 60002
		5g. IRB Protocol Number:
		8. PERFORMING ORGANIZATION REPORT NUMBER Report No. 01-19
		10. Sponsor/Monitor's Acronyms(s) BuMed
		11. Sponsor/Monitor's Report Number(s)

12 DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release; distribution unlimited.

13. SUPPLEMENTARY NOTES
Published in Navy Medicine, 2001, 92(4), 6-9

14. ABSTRACT (maximum 200 words)

Gulf War veterans in the San Diego area were given an important opportunity to help researchers learn how to treat chronic multi-symptom illnesses. The Department of Defense (DOD) Center for Deployment Health Research at the Naval Health Research Center, San Diego, is participated in two large clinical trials to treat nonspecific illnesses among Gulf War veterans. One of more than 30 sites nationwide, the Naval Health Research Center is the only Navy site involved in these Department of Veterans Affairs (VA)-DOD cooperative studies. Other sites include the Walter Reed Army Medical Center, Washington, DC, and 28 VA medical centers across the country. Two VA-DOD Cooperative studies were used: #470, Exercise and Cognitive Behavioral Therapy Trial and #476, Antibiotic Treatment Trial.

14. SUBJECT TERMS
child sexual abuse; research methodology

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGE 4	18a. NAME OF RESPONSIBLE PERSON Commanding Officer
a. REPORT	b. ABSTRACT	c. THIS PAGE			18b. TELEPHONE NUMBER (INCLUDING AREA CODE) COMM/DSN: (619) 553-8429
UNCL	UNCL	UNCL	UNCL		