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A Comprehensive Clinical Evaluation of 20,000 Persian Gulf War Veterans

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In response to the health concerns of Gulf War veterans, the Department of Defense instituted the Comprehensive Clinical Evaluation Program (CCEP). Although not designed as a research study, the CCEP provided valuable clinical data. An analysis was conducted of CCEP findings from systematic and comprehensive examinations of 20,000 U.S. Gulf War veterans. Among 20,000 participants, the types of primary and secondary diagnoses varied widely. Also, among veterans with an ICD-9-CM diagnosis of "symptoms, signs, and ill-defined conditions," no single subcategory of illness predominated, and no characteristic physical sign or laboratory abnormality was identified. In total, there were 74 (0.4%) cases of connective

tissue disease; 52 (0.3%) noncutaneous malignancies; 42 (0.2%) peripheral neuropathies; 14 (0.07%) cases of interstitial pulmonary fibrosis; 12 (0.06%) cases of renal insufficiency; and no new cases of viscerotropic leishmaniasis. No clinical indication of a new or unique illness was identified in this self-referred population, and the types of physiologic disease that could result from postulated hazardous wartime exposures were uncommon.

Introduction

During the 6 years since the end of the Persian Gulf War on February 28, 1991, some veterans of Operations Desert Shield and Desert Storm have presented with a diversity of unexplained somatic symptoms. The most commonly reported symptoms have been fatigue, headache, joint pains, skin rash, shortness of breath, sleep disturbances, difficulty concentrating, and forgetfulness.¹⁻³ There have been published medical reports of similar symptoms among British and Canadian Gulf War veterans but not among other coalition troops or local inhabitants of Saudi Arabia and Kuwait.⁴⁻⁶

To date, no single cause of these somatic symptoms has been demonstrated.⁷⁻¹¹ However, various potential etiologies related to the Gulf War experience have been postulated, including: (1) possible exposure to chemical weapons (CW) and biological weapons (BW);^{8-10,12-14} (2) use of pyridostigmine bromide pills for CW protection;^{7,8,15} (3) exposure to sand and oil well fire smoke;^{8,16} (4) exposure to pesticides, insect repellents, and other chemicals used in military deployments;^{9,14,17,18} (5) anthrax and botulinum vaccinations;⁷⁻⁹ (6) infectious diseases, particularly viscerotropic leishmaniasis;¹⁹ (7) depleted uranium exposure;⁷⁻⁹ and (8) psychological stress.^{11,20-23}

In response to the health concerns of Gulf War veterans, the Department of Defense (DoD) instituted the Comprehensive Clinical Evaluation Program (CCEP) on June 7, 1994. The CCEP was a continuation of prior DoD medical care of Gulf War veterans and screening for new or unusual illnesses but provided a more systematic evaluation strategy. Although not designed as a

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research study, the CCEP nevertheless provided valuable clinical information about the health of this population. The following report is an analysis of the findings from comprehensive clinical evaluations of 20,000 Persian Gulf War veterans.

Methods

Background

Starting on August 8, 1990, the United States deployed 697,000 troops to the Persian Gulf region.⁸ In contrast to previous U.S. conflicts, a larger proportion of troops belonged to the Reserves/National Guard (17%) and were women (7%). Despite the harsh environment and intense preparations for war,²⁴ morbidity rates among U.S. troops were lower than in previous conflicts,^{8,25,26} and mortality rates were very low.²⁷

By May 1991, most U.S. troops had returned from the Persian Gulf. Troops who remained on active duty after the war were provided complete health care through the Military Health Services System, which provides medical care for all active duty personnel and other eligible DoD beneficiaries. In addition, the physical condition of active duty U.S. troops is assessed continuously with physical fitness tests every 6 to 12 months, routine dental and gynecological examinations, and a complete medical examination at least every 5 years. Prior to leaving active duty, military personnel are medically screened and undergo a physical examination.

CCEP Organization

The CCEP was developed to provide a systematic and uniform medical evaluation at 184 military health care facilities located in 39 states, 8 foreign countries, and 2 territories. To institute the CCEP, numerous organizational meetings were held with senior medical officials from all military services; health care officials of the Department of Veterans Affairs (VA) were consulted to ensure that the CCEP and the VA Persian Gulf Health Registry collected comparable data; and four instructional meetings were held with military health care personnel on CCEP procedures and to provide clinical and research information related to Gulf War health questions. A special committee of the Institute of Medicine independently reviewed and monitored the CCEP process, including the design and implementation of the program and interpretation of preliminary findings.²⁸

Through vigorous outreach efforts, the 285,000 Persian Gulf War veterans still on active duty when the CCEP was initiated were encouraged to participate if they had any health questions or concerns; a current health problem was not necessary for participation. Also eligible were military retirees, Reserve / National Guard personnel on full-time active duty or on special orders, and civilian DoD employees who were veterans of the Persian Gulf deployment. Family members of qualified Gulf War veterans were eligible for CCEP evaluation but were not included in this analysis.

Eligible veterans could enroll in the CCEP either by calling a toll-free telephone number or by contacting their nearest military medical treatment facility (MTF). Gulf War veterans not eligible for a CCEP examination were referred to the VA Persian Gulf Health Registry for evaluation.

Clinical Evaluation

The CCEP provided a two-phase clinical evaluation supervised by a board-certified physician in either family practice or

internal medicine.²⁹ All CCEP participants were provided a Phase I examination, which was conducted at the local MTF and consisted of a thorough clinical examination and a standardized provider-administered questionnaire. All participants were asked about: (1) medical and family histories; (2) symptoms; (3) number of days of work lost due to illness during the 90 days prior to examination; and (4) any self-perceived exposure in the Persian Gulf to among the following: petroleum products, pyridostigmine bromide pills, oil well fire smoke, insect repellents, anthrax and botulinum vaccinations, combat casualties, and actual combat. In addition, the following laboratory tests were performed: a complete blood count, urinalysis, and blood chemistries for electrolytes, glucose, creatinine, blood urea nitrogen, and transaminase levels.

For CCEP participants without current medical problems or who had health problems that could be satisfactorily explained after the Phase I evaluation, no additional evaluation was conducted. Other CCEP participants proceeded to further Phase II examination at one of 14 DoD regional medical centers, if referral consultations and specialized tests were clinically indicated, to diagnose the patient's condition. Phase II participants were administered the Structured Clinical Interview for DSM-III-R³⁰ and the Clinician Administered PTSD Scale.³¹ Additionally, Phase II participants had a purified protein derivative skin test and chest X-ray, and a blood sample was analyzed for the following: sedimentation rate, C-reactive protein, rheumatoid factor, fluorescent antinuclear antibodies, thyroid function, B 12 and folate levels, creatine phosphokinase level, HIV-I antibody, hepatitis B surface antigen, and reagin antibody.²⁸

At the conclusion of the CCEP evaluation process, examining physicians provided a primary diagnosis and additional secondary diagnoses based on clinical importance. After review by accredited medical record coders, up to seven diagnoses were coded using the International Classification of Diseases-Ninth Revision, Clinical Modification (ICD-9-CM) and entered into the data base.³² An extensive quality-control process was instituted to ensure uniform evaluation, accurate data collection, and data base validity.²⁸

Results

As of April 1, 1996, a total of 20,000 Persian Gulf War veterans had completed CCEP examinations, with 12% of participants undergoing specialized Phase II evaluations. Compared to all US. Gulf War veterans, the CCEP included a higher proportion of women, older veterans, nonwhite racial/ethnic groups, and Army personnel (Table I).

The types of primary and secondary diagnoses among CCEP participants varied widely (Table II). A total of 1,263 separate ICD-9-CM codes were needed to categorize primary diagnoses. Of the 1,263 separate codes used, 41% were applicable to only a single CCEP participant. Relatively frequent primary diagnoses (shared by 25 or more veterans) were distributed among 114 different ICD-9-CM codes.

For broad ICD-9-CM classifications, the three most common primary diagnoses were "diseases of the musculoskeletal system and connective tissue" in 18.6%, "mental disorders" in 18.3%, and "symptoms, signs, and ill-defined conditions" in 17.8% of participants (Table II). Nine percent of participants were found to be "healthy," without a clinically significant new

TABLE I
COMPARISON OF DEMOGRAPHIC CHARACTERISTICS BETWEEN
20,000 CCEP PARTICIPANTS AND ALL U. S. PERSIAN GULF
WAR VETERANS

Characteristic	Percent with Characteristic	
	CCEP Participants ^a (n = 20,000)	All Gulf War Veterans (n = 697,000)
Gender		
Male	88	93
Female	12	7
Age in years ^b		
17-25	32	55
26-30	24	20
31-35	23	12
36-65	21	13
Race / ethnicity		
White	57	70
African-American	32	23
Hispanic	5	5
Other	6	2
Rank		
Enlisted	92	90
Officer	8	10
Military branch		
Army	82	50
Navy	4	23
Marines	4	15
Air Force	9	12
Military status		
Active duty	84	83
Reserves/National Guard	8	17
Civilians	8	-

^aAmong CCEP participants, valid data were not available for 3% of rank, 2% of age, and 1% of military branch entries.

^bAge was calculated as of August 1990. The mean age of CCEP participants was 28 years (median 30 years) compared to a mean age of 27 years (median 25 years) for all Gulf War veterans.

illness. The most common specific diagnoses among patients with a primary diagnosis of a musculoskeletal disease were "pain in joint" (31%), "osteoarthritis and allied disorders" (12%), and "lumbago" and "backache, unspecified" (11%). Among veterans with a primary diagnosis of "mental disorders," 19% had "tension headache," 17% "depressive disorder not elsewhere classified," 15% "prolonged post-traumatic stress disorder" (PTSD), 8% "major depressive disorder, single episode," and 7% "adjustment reaction."

Among the 3,558 participants with a primary diagnosis of "symptoms, signs, and ill-defined conditions," no single ICD-9-CM subcategory predominated (Table III). These 3,558 veterans had a wide variety of symptoms, with fatigue, headache, memory problems, and sleep disturbances being the most frequent presenting complaints (Table IV). Symptoms were reported to have begun more than 6 months after returning from the Persian Gulf by 51% of the 1,026 veterans in this category who indicated a date of onset. Veterans with this primary diagnosis did not have a characteristic sign of disease (including skin rash and fever) or a consistent laboratory abnormality. Also, no distinctive pattern of illness was evident among CCEP participants with this ICD-9-CM code as a secondary diagnosis (Table III).

There were a number of age, gender, and military service trends among broad primary diagnostic classifications. Mental disorders and a diagnosis of "healthy" were more common among younger CCEP participants (Table V). Musculoskeletal conditions were diagnosed more often in older participants (Table V), males (19% compared to 16% among females), and U.S. Army personnel (19% compared to 16% among other services). Women were more likely to be diagnosed with genitourinary problems than men (3% vs. 1%, respectively). Eighty percent of CCEP participants reported not missing any days of work during the 90 days prior to examination.

Among all 20,000 CCEP participants, 74 (0.4%) had a connective tissue disease as either a primary or secondary diagnosis: 33 rheumatoid arthritis, 13 systemic lupus erythematosus, 13 Sjogren's syndrome, 10 mixed or undifferentiated connective tissue disease, 3 systemic sclerosis, and 2 dermatomyositis. Disorders of immunity were diagnosed in 5 participants with selective immunoglobulin A immunodeficiency and one with selective immunoglobulin M immunodeficiency. There were 9 (0.05%) patients who had skin cancers, 22 (0.1%) lymphoma/leukemia, and 30 (0.15%) other types of cancer. Glomerulonephritis was diagnosed in **13 (0.07%)** CCEP participants and renal insufficiency in another **12** patients. Fourteen (0.07%) participants had interstitial pulmonary fibrosis.

Polyneuropathy or peripheral neuropathy was diagnosed in 8 and 34 (0.2%) veterans, respectively. A common or distinctive organic pathology was not identified among over 800 veterans with neuromuscular symptoms who had extensive neuropsychological evaluations. These evaluations included nerve conduction studies and electromyography on 300 participants³³ and intensive electrophysiological studies (including single-fiber electromyography and muscle biopsies) on 20 veterans with severe fatigue, weakness, or myalgias.³⁴

Common skin infections accounted for 60% of primary infectious disease diagnoses (Table II). Four CCEP participants without characteristic clinical signs of Q fever had minimally elevated serologic titers to *Coxiella burnetii*. There were no confirmed cases of brucellosis, and no new case of viscerotropic leishmaniasis was diagnosed in addition to the **12** previously identified cases.

All elicited exposures were reported frequently, including: exposure to diesel and other fuels (88%); use of pyridostigmine bromide pills (74%); exposure to oil well fire smoke (71%); personal use of insect repellents (66%); anthrax (49%) and botulinum (26%) vaccinations; and observing combat casualties (57%) or actual combat (38%). Independent records were not available to assess self-reported exposures except for botulinum vaccination, which was known to have been given to about 1.1% of troops, mostly in select front-line units. In the broad ICD-9-CM diagnostic categories, there were no major differences in the percentage of CCEP participants reporting various exposures.

Discussion

This large patient series demonstrated a wide range of well-known illnesses among Persian Gulf War veterans requesting evaluation, with no single illness predominating and no clinical indication of a new or unique syndrome. In addition, the types of medical conditions that would result from postulated Gulf War environmental hazards were diagnosed infrequently, including:

TABLE II
FREQUENCY OF PRIMARY AND SECONDARY DIAGNOSES BY BROAD ICD-9-CM CATEGORIES AMONG 20,000 CCEP PARTICIPANTS

Category	ICD-9-CM Code	Primary Diagnosis	Secondary Diagnoses
Diseases of the musculoskeletal system and connective tissue	710-739	18.6	29.5
Mental disorders	290-319	18.3	17.9
Symptoms, signs, ill-defined conditions	780-799	17.8	32.6
Diseases of the respiratory system	460-519	6.8	10.8
Diseases of skin and subcutaneous tissue	680-709	6.3	13.7
Diseases of the digestive system	520-579	6.2	14.1
Diseases of nervous system and sense organs	320-389	5.8	12.3
Infectious and parasitic diseases	001-139	2.6	6.4
Diseases of the circulatory system	390-459	2.2	5.9
Endocrine, nutritional, and metabolic diseases, and immunity disorders	240-279	2.1	6.1
Diseases of the genitourinary system	580-629	1.3	4.2
Injury and poisoning	800-999	0.8	2.4
Neoplasms	140-239	0.8	2.1
Diseases of the blood and blood-forming organs	280-289	0.6	2.6
Congenital anomalies; certain conditions originating in the perinatal period	740-779	0.2	0.9

TABLE III
FREQUENCY OF SPECIFIC DIAGNOSTIC SUBCATEGORIES AMONG CCEP PARTICIPANTS WITH PRIMARY OR SECONDARY DIAGNOSES OF "SYMPTOMS, SIGNS, AND ILL-DEFINED CONDITIONS" (ICD-9-CM CODE 780-799)

Diagnostic Subcategory	ICD-9-CM Code	Percent (number) with Primary Diagnosis (n = 3,558)	Percent (number) with Secondary Diagnosis (n = 9,254) ^a
Malaise and fatigue	780.7/780.71	26.6 (948) ^b	17.9 (1,656)
Sleep disturbances	780.50152157	17.6 (627)	14.2 (1,310)
Headache	784.0	14.7 (524)	14.5 (1,342)
Other general symptoms	780.9	10.3 (366)	13.0 (1,200)
Dyspnea and respiratory abnormalities	786.09/786.52	5.7 (204)	7.3 (676)
Symptoms involving skin	782.0/782.1	4.8 (171)	5.3 (487)
Syncope / convulsions / dizziness	780.21314	2.9 (102)	1.9 (175)
Chest pain	786.50/786.59	2.1 (75)	2.0 (189)
Nonspecific reaction to tuberculin test	795.5	1.3 (47)	3.3 (309)
Abdominal pain	789.0	1.3 (48)	1.5 (135)
Cough	786.2	1.1 (38)	0.9 (80)
Other subcategories	-	11.5 (408)	18.3 (1,695)

^a9,254 secondary diagnoses in the category of "Symptoms, Signs, and Ill-Defined Conditions" among 6,517 individual CCEP participants.

^b297 with chronic fatigue and 651 with fatigue not specified as chronic.

neurologic disease from possible CW or pesticide exposure, interstitial pulmonary disease from smoke or sand inhalation, renal disease from heavy metal exposure, and immunologic dysfunction from various combinations of exposures.

These findings are consistent with medical surveillance data collected during the Persian Gulf deployment, which indicated that the overall health of US troops was very good;^{8,27} serious illness due to pyridostigmine bromide or smoke inhalation was uncommon;³⁵⁻³⁷ and clusters of acute disease compatible with either pesticide intoxication or a CW/BW attack were not diagnosed.^{8,9,38} Also, the absence of clinical data indicating a new or unique illness is consistent with the findings of three previous review panels that did not identify a distinctive syndrome related to Persian Gulf service.^{7,8,11}

A relatively large percentage of CCEP participants did have a psychological condition as either a primary (18%) or secondary (18%) diagnosis. This finding was not unexpected because transient and mild psychological conditions are common in out-patient populations,³⁹ and studies of military veterans repeatedly have

demonstrated that adjustment reaction and PTSD are prevalent following life-threatening wartime experiences.⁴⁰⁻⁴² Prior studies additionally have found that the types of physical symptoms, sleep problems, and cognitive difficulties experienced by some Gulf War veterans are frequent manifestations of psychological stress related to war⁴²⁻⁵⁵ and other traumatic events.^{56,57}

Also expected among CCEP participants was a large number of musculoskeletal conditions, because this was predominantly an active duty military population that constantly is undergoing physically demanding training.⁵⁸ The increased risk of genitourinary problems among female veterans has been found in prior studies of US military populations.⁵⁹

The third common diagnostic category, "symptoms, signs, and ill-defined conditions," did not appear to represent a group of veterans with a distinctive illness. CCEP participants in this diagnostic category varied substantially in clinical presentation, and no characteristic physical sign or laboratory abnormality was identified. The ICD-9-CM category "symptoms, signs, and ill-defined conditions" is not a classification of a mystery ill-

TABLE IV

THE MOST FREQUENT SYMPTOMS AMONG 3,558 CCEP PARTICIPANTS WITH A PRIMARY DIAGNOSIS OF "SYMPTOMS, SIGNS, AND ILL-DEFINED CONDITIONS" (ICD-9-CM CODE 780-799)

Symptoms	Percent Reporting Symptom ^a	
	Chief Complaint	Any Complaint
Fatigue	20.0	59.0
Headache	9.2	44.4
Memory problems	6.3	40.3
Sleep disturbances	4.7	39.8
Skin rash	4.4	30.2
Joint pain	4.2	47.0
Dyspnea	1.8	19.2
Cough	1.3	1.3
Abdominal pain	1.2	16.3
Muscle pain	0.8	21.8
Difficulty concentrating	0.6	31.2
Back pain	0.6	0.6
Dizziness	0.6	0.6
Diarrhea	0.5	18.4
Hair loss	0.1	12.6
Weight loss	0.2	6.9
Bleeding gums	0.1	8.5
Depression	0.3	22.3
Other symptoms	17.3	21.4

^aSymptoms without a designation of a chief complaint were recorded for 914 (26%) participants.

ness.³² This diverse category contains more than 160 subclassifications and mainly consists of: ill-defined, often common conditions not coded elsewhere (such as nervousness); isolated laboratory abnormalities (such as "nonspecific reaction to tuberculin test"); and common symptoms without a clear physiologic or psychologic basis. The somatic symptoms specifically coded in this classification—insomnia, fatigue/malaise, headache, dyspnea, palpitations, heartburn—are reported very frequently in general population⁶⁰ and outpatient clinic surveys.⁶¹⁻⁶³ These symptoms, although genuine and sometimes the cause of substantial morbidity, often lack a physical explanation or are related to psychological factors.⁶³⁻⁶⁸

These clinical findings have to be carefully qualified by the fact that the CCEP was not designed as a research study: participants were self-selected and physically qualified for active military duty several years after the Persian Gulf War, and no control group was available for comparison of illness rates. In

addition, a rare or minimally pathogenic illness could have been missed²⁸ or not adequately captured in the data base because of diagnostic weaknesses of the ICD-9-CM coding system. Nevertheless, any widespread, serious physiologic disease should have been detected in this very large patient series. It also is unlikely that debilitating disease would remain undetected among active duty troops not participating in the CCEP because of the military's emphasis on readiness and preventive medicine, with regular physical evaluations of troops.

Because the CCEP primarily involved active duty troops, an illness that predominated among Reserve/National Guard personnel or veterans who had been discharged from the military would have been under-represented in the CCEP population. However, no new or unique illness has been identified in the VA Persian Gulf Health Registry, which primarily includes Reserve / National Guard personnel and discharged troops.^{9,69} Together, the DoD and VA registry programs have evaluated more than 13% of all U.S. Persian Gulf War veterans for illnesses potentially related to Persian Gulf service.

Although a new or unique illness was not identified, the findings of the CCEP nevertheless provide important clinical information. In the evaluation of Persian Gulf War veterans, physicians will need to be alert for a wide range of illnesses because the diversity of medical and psychological problems that occur in any sizable adult population was found in this cohort. In addition, the findings of the CCEP provide reassurance for Persian Gulf veterans since effective treatments are available for most commonly diagnosed health problems.

Inability in this and prior clinical evaluations to find a characteristic organic sign of a new or unique disease among Persian Gulf veterans will result in research limitations not encountered in studies of well-characterized diseases.^{1,3,9,70} Most importantly, a specific case-definition based on criteria that can be objectively measured cannot be developed without a characteristic sign of pathology. Any definition of illness will have to be based on self-reported symptoms, which are subject to confounding and recall bias in a population that has been the focus of widespread publicity about possible harmful exposures and ill health.⁷¹⁻⁷⁶ In addition, because of wartime conditions, there are limited records available to quantitate potentially hazardous exposures.^{8,9}

Although there are methodological limitations in conducting studies of a possible disease related to the Gulf War, studies of well-characterized disorders can provide vital information about the health of Gulf War veterans. Preliminary research results

TABLE V

AGE TRENDS FOR BROAD PRIMARY ICD-9-CM DIAGNOSTIC CATEGORIES AMONG 20,000 CCEP PARTICIPANTS^a

Diagnostic Category	ICD-9-CM Code	Percent with Diagnosis by Age Range in Years ^b				
		17-20	21-25	26-30	31-35	>35
Mental disorders (non-PTSD)	290-319	18	16	15	15	14
PTSD	309.8 1	4	3	3	2	3
Ill-defined conditions	780-799	16	18	18	18	18
Musculoskeletal diseases	710-739	15	17	18	21	20
Other ICD-9-CM categories	-	35	35	36	36	38
"Healthy"	-	13	11	10	8	7

^aAges are as of August 1990.

^bValid age data were not available for 422 (2.1%) participants.

indicate that this population has normal pulmonary function,⁷⁷ has not experienced higher mortality or hospitalization rates from medical causes,^{78,79} and has not had higher overall rates of birth defects among its children.^{80,81} Several studies indicate that Gulf War veterans have experienced increased levels of psychological stress,^{20-23,82-88} with between 5 and 16% of surveyed veterans having symptoms of PTSD.^{20,84,86}

Six years after the Persian Gulf War, veterans' health questions remain unresolved because the causes, frequency, and long-term sequelae of nonspecific somatic symptoms are not adequately understood.^{62,89-91} Because symptoms of fatigue, headache, joint pain, and insomnia are experienced by all adult populations, it is difficult to determine when these symptoms represent transient conditions or are manifestations of either occult organic or psychologic illness.⁹⁰⁻⁹³ Even when somatic symptoms appear to constitute a distinctive syndrome, such as chronic fatigue syndrome and fibromyalgia, specific case-definitions have not been developed and etiologic factors remain undetermined despite more than a decade of intensive investigation.⁹⁴ Until the nature of nonspecific symptoms and illnesses such as chronic fatigue syndrome is better understood, it will not be possible to thoroughly determine the health of any large population, whether military or civilian.⁹⁵

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