- six projects (one human controlled-exposure study and five animal studies) related to *toxicity of pyridostigmine bromide*;
- and numerous clinical and epidemiological studies related to *assessment and definition of Gulf War illnesses* and quantification of *disease prevalence and associations between chemical exposures and disease*.

5. Gulf War Illnesses: Research Results and Ongoing Research

This section discusses results from research related to illnesses in Gulf War veterans and relationships of the results to ongoing research projects. Included in the discussion are results from mortality and hospitalization studies, studies of self-reported symptoms in Gulf War-deployed and non-deployed veterans, studies of neurophysiological and neuropsychological variables in symptomatic Gulf War veterans, studies of health effects from mixtures of chemicals used in the Gulf War and other risk factors, studies of genetic differences in susceptibility to environmental agents, studies of multiple chemical sensitivity in Gulf War veterans, and studies of treatment of Gulf War veterans with non-specific chronic symptoms of ill health. Appendix C: *Research on Gulf War Illnesses: Description and Evaluation of Selected Studies* and Appendix D: *Ongoing Research Related to Illnesses Among Gulf War Veterans* provide additional details.

Mortality and Hospitalization Studies

Large-scale studies are available comparing the following in active-duty U.S. military personnel who served in the Gulf War with active-duty personnel who did not serve in the Gulf :

- rates of mortality (Writer et al., 1996; Kang and Bullman, 1996, 1997);
- rates of general hospitalizations (Gray et al., 1996);
- rates of hospitalizations for unexplained illnesses (Knoke and Gray, 1998);
- rates of hospitalization for testicular cancer (Knoke et al., 1998); and
- rates of general birth defects and a specific birth defect, Goldenhar syndrome (Cowan et al., 1997; Aranata et al., 1997).

The mortality rate studies found no differences between Gulf War-deployed and non-deployed personnel, except for a higher rate of mortality from unintentional injuries (i.e., accidents, in particular motor vehicle accidents) in deployed personnel (Writer et al., 1996; Kang and Bullman, 1996, 1997). The hospitalization studies, which focused on discharge rates from U.S. military hospitals, found no consistent evidence for increased hospitalizations in Gulf War-deployed personnel (Gray et al., 1996; Knoke and Gray, 1998; Knoke et al., 1998). The studies of children of deployed-personnel born in U.S. military hospitals found no statistically significant increase in

general birth defects or in Goldenhar syndrome[5] compared with children born to non-deployed personnel (Cowan et al., 1997; Aranata et al., 1997).[6]

Whereas these large-scale studies have not found evidence for increased incidence of grave illness among Gulf War veterans, they have several limitations including: not studying personnel who separated from the military; not studying geographically or exposure-defined subgroups; not examining non-military hospitalizations; and not examining outpatient treatment of illness (see Appendix C for more discussion). These studies, thus, do not negate the fact that Gulf War veterans have experienced, and still are experiencing, real illnesses, as demonstrated by the DVA and DoD clinical experiences. Discussion of the strengths and limitations of the published mortality, hospitalization, and reproductive-outcome studies are available in the literature (Doyle et al., 1997; Haley, 1998a,b; Kang and Bullman, 1998; Gray et al., 1998; Cowan et al., 1998). With respect to the possibility that reproductive outcomes (e.g., increased risk for fetal deaths, birth defects, miscarriages, medical termination of pregnancy, and infertility) might be influenced by Gulf War service, there are several on-going controlled epidemiological studies that were designed with these limitations in mind, but for which data are not yet available (see Doyle et al., 1997; RWG, 1997, 1998, 1999; Cowan et al., 1998).

Studies of Self-reported Symptoms in Gulf War-Deployed and Non-deployed Veterans

Results from several studies are available comparing self-reported health symptoms and medical conditions in groups of Gulf War deployed and non-deployed veterans (CDC, 1995; Fukuda et al., 1998; Iowa Persian Gulf Study Group, 1997; Stretch et al., 1995; Pierce, 1997; Canadian Department of National Defence, 1998; Unwin et al., 1999; Ismail et al., 1999; Proctor et al., 1998). These studies have found consistently higher rates of self-reported symptoms in deployed compared with non-deployed veterans; short descriptions of results follow. Results from these studies should be evaluated with the generally accepted understanding that self-reported symptoms are subject to individual and group biases ("recall biases") that can distort the magnitude of differences between groups. (More study details are included in Appendix C)

The CDC (1995) compared rates of self-reported health symptoms that persisted for more than six months among Gulf War deployed and non-deployed, active-duty personnel in Air Force units

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[5] Goldenhar syndrome is a prenatal developmental disorder that leads to abnormal ear and facial structures; anecdotal reports in the popular press in 1995 suggested that there might be an excess of this birth defect among children of Gulf War veterans (Aranata et al., 1997).

[6] In addition to these studies of active-duty personnel, early news-media reports that there was an apparent cluster of birth defects in Gulf-deployed Mississippi National Guard units were not supported by a subsequent examination of the frequencies of birth defects, low-birth weight, or premature births in 54 of 55 children born to 52 veterans in these units compared to U.S. national rates, but the small sample size in this study does not allow a definitive conclusion that applies to all Gulf War veterans (Penman et al., 1996).

from Pennsylvania and Florida and found that the prevalence of each of thirteen symptoms[7] was significantly greater in deployed personnel compared with non-deployed personnel. Individuals in a sample of this study population were defined either as "cases" with chronic multiple symptoms or "noncases" based on their survey responses[8] and evaluated further in physical examinations, laboratory tests of blood, stool and urine samples, and serological examinations (Fukuda et al., 1998). Fukuda et al. (1998) reported that: 1) "cases" with chronic multiple symptoms were more frequent in the deployed group compared with the non-deployed group; 2) no findings in the physical, laboratory or serological tests were predictive of case definition[9]; and 3) no significant associations were found between having chronic multiple symptoms and several surrogate measures of exposure (e.g., date of deployment, season of deployment, occupational activity during war).

The Iowa Persian Gulf Study Group (1997) found significantly higher prevalence of similar self-reported symptoms indicative of several syndromes or disorders[10] in a group of Gulf War-deployed personnel from Iowa who served in U.S. regular military, National Guard, or reserve units compared with a similar group of non-deployed military personnel from Iowa. Stretch et al. (1995; 1996a,b) also found significantly higher percentages of self-reported physical health symptoms in Gulf-deployed veterans from Hawaii and Pennsylvania compared with non-deployed veterans, and noted that this difference was not explained by several demographic variables (e.g., age, rank, marital status) other than deployment.

In a study of female U.S. veterans, Pierce (1997) reported that self-reported frequencies of occurrence of general health symptoms[11] were higher in deployed versus non-deployed veterans, but the differences were not statistically significant. However, self-reported frequencies of occurrence of other symptoms[12] (lumps or cysts in breasts, abnormal Pap smear, headache) were statistically significantly higher, four years after the war, in deployed veterans than in non-deployed veterans, and a significantly greater percentage of deployed veterans (24%) met the

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[7] For example: fatigue, joint pain, nasal congestion, diarrhea, joint stiffness, unrefreshing sleep.

[8] A case was defined as reporting one or more chronic symptom from at least two of three categories: fatigue, mood-cognition and musculoskeletal.

[9] Fukuda et al. (1998) reported that "mean values of a few routine blood tests differed among cases and noncases, but the differences were marginal and clinically unimportant". They noted that a more detailed summary of blood and urine data was available by request.

[10] For example: depression, posttraumatic stress disorder, chronic fatigue, cognitive dysfunction, asthma, and fibromyalgia.

[11] Rash, cough, depression, unintentional weight loss, insomnia and memory problems.

[12] Pierce (1997) termed these symptoms *gender specific*.

requirement for combat-related posttraumatic stress disorder (PTSD) than non-deployed veterans (15%) (Pierce, 1997).

In a study of self-reported health symptoms in Canadian Gulf War veterans compared with non-Gulf-deployed Canadian veterans, Gulf-deployed veterans reported higher prevalences of symptoms of chronic fatigue, cognitive dysfunction, multiple chemical sensitivity, major depression, post-traumatic stress disorder, anxiety, fibromyalgia and respiratory diseases (bronchitis and asthma together), as well as higher numbers of children with birth defects (before, during, and after the Gulf War) (Canadian Department of National Defence, 1998).

Investigators at the Boston Environmental Hazards Center found significantly higher percentages of veterans who reported health symptoms[13] in Gulf-deployed groups from New England (n= 186) and New Orleans (n = 66) compared with a group of U.S. veterans (n = 48) who were deployed to Germany during the Gulf War period (Proctor et al., 1998). Statistical analysis of symptom scores (that were based on self-reported frequency of occurrence of the symptoms) and self-reported military-experience exposures found significant associations between specific symptoms[14] and exposures to pesticides, debris from Scud missiles, chemical or biological warfare agents, and smoke from tent heaters.

In a survey study of U.K. veterans, significantly higher percentages of Gulf-deployed veterans reported numerous health symptoms[15] compared with non-deployed veterans from the same era or veterans deployed to Bosnia (Unwin et al., 1999). Most of these differences persisted after statistical adjustment for possible confounders and diagnosed psychological disorders. Statistical associations between self-reported symptoms and self-reported exposures to numerous health risk factors[16] were examined in each of the studied groups, after defining individuals with multiple

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[13] Skin rashes, stomach cramps or excessive gas, joint pains, headaches, difficulties learning new material, inability to fall asleep, and frequent periods of anxiety or nervousness.

[14] The analysis excluded 12 subjects in the Gulf-deployed groups who were diagnosed with current PTSD. Statistically significant associations included those between: 1) self-reported exposure to pesticides and musculoskeletal or neurological symptoms; 2) self-reported exposure to debris from Scud missiles and musculoskeletal, neurological, neuropsychological or psychological symptoms; 3) self-reported exposure to chemical or biological warfare agents and musculoskeletal, neurological, neuropsychological, and psychological symptoms; and 4) self-reported exposure to smoke from tent heaters and cardiac, neurological, and pulmonary symptoms.

[15] For example, fatigue, sleep disturbances, irritability, headaches, loss of concentration, joint stiffness or pain, tingling in fingers and arms, chest pain, and night sweats

[16] For example, smoke from oil-well fires, use of personal pesticides, use of pyridostigmine bromide, belief of exposure to chemical attack, multiple routine vaccinations, or vaccinations for biological warfare agents.

symptoms[17] as "cases" and others as "noncases". In all three groups of veterans, statistically significant associations were found between reporting multiple symptoms and reporting exposure to numerous agents, including nerve gas, exhaust from heaters or generators, and pyridostigmine bromide. A weak, although statistically significant, association between reporting multiple symptoms and reporting receiving multiple vaccinations was found in the Gulf-deployed U.K. veterans, but not in the Bosnia U.K. veterans (Unwin et al., 1999). In a companion study, Ismail et al. (1999) used a mathematical technique, two-step factor analysis, to examine if the self-reported symptoms represented a unique Gulf War disorder. Using this technique, a three-factor structure was identified among the Gulf-deployed veterans; the "factors" were labeled mood, respiratory system and peripheral nervous system based on their defining symptoms. Ismail et al. (1999) reported that this three-factor structure also reasonably fit the Bosnia-deployed veterans and the non-deployed, Gulf War-era veterans, and concluded that their findings do not support a unique Gulf War syndrome.

Other studies also looked for relationships between self-reported health symptoms and measures of stress or self-reported exposures to specific health risks such as combat, poisonous gas or occupational exposure to petroleum products (Stretch et al., 1996a,b; Baker et al., 1997; Wolfe et al., 1998). Relationships between war-related stress and physical symptoms of ill-health were found (Stretch et al., 1996a,b; Baker et al., 1997), but these studies do not indicate the strength of the relationship and do not exclude possible relationships between symptoms and other risk factors. One study found that, in a group of Gulf-deployed U.S. veterans, self-reported exposure to poisonous gas was related to higher symptom reporting (Wolfe et al., 1998).

Based on the results of several psychological tests, Stretch et al. (1996a,b) reported that, in addition to more frequently reporting health symptoms, deployed veterans from Hawaii and Pennsylvania exhibited more stress than non-deployed veterans. In a study of 188 Gulf War veterans, half of whom were patients at the Cincinnati Veterans' Administration Medical Center, Baker et al. (1997) found that the 24 Gulf War veterans in this group with PTSD had statistically significantly greater combat exposure and reported more symptoms than others in the group. Wolfe et al. (1998) found that, in a study of 2,119 Gulf-deployed troops who returned to the U.S. through Fort Devens, veterans who reported having been exposed to poison gas were more likely to report health symptoms (such as aches/pains, lack of energy, etc.), even after excluding from the analysis those subjects with presumptive PTSD, and that deployed veterans with combat exposure or occupational exposure to motor vehicles (i.e., petroleum products) were not more likely to report health symptoms.

As discussed earlier, an on-going large-scale project, the VA National Health Survey, is designed to estimate and compare the prevalence of various symptoms, medical conditions, and unexplained illnesses in Gulf War-deployed and non-deployed U.S. veterans and look for relationships between exposure to specific risk factors and frequencies of health symptoms (DVA

[17] Following the convention of Fukuda et al. (1998), a case was defined as reporting one or more chronic symptom from at least two of three categories: fatigue, mood-cognition and musculoskeletal.

research project #2; RWG, 1998, 1999). Data from this project are not currently available. Other on-going large-scale projects for which data are not yet available include:

- a University of Oregon study comparing health survey responses and clinically evaluated neuropsychological and neurophysiological variables in: subjects from U.S. troops located within a 50-km radius of Khamisiyah in March, 1991; subjects from other U.S. Desert Storm and Desert Shield troops; subjects from other U.S. troops that were not deployed to the Gulf region; and civilians with a documented history of exposure to organophosphate insecticides (DoD research project #63; RWG, 1998, 1999); and
- an Institute of Medicine/Medical Follow-up Agency study comparing hospitalization rates and mortality rates during a 5-year post-Gulf War period in: subjects directly involved in the March 1991 Khamisiyah demolition, subjects from two battalions located within a 50-km radius of the Khamisiyah demolition site during March, 1991; subjects from Gulf War battalions never located within a 50-km radius of Khamisiyah; and subjects from non-deployed U.S. troops (DoD research project #69; RWG, 1998, 1999).

Neurophysiological and Neuropsychological Evaluations of Symptomatic Gulf War Veterans

Several studies have carried out neurophysiological and neuropsychological evaluations of small groups of symptomatic Gulf War veterans (Jamal et al., 1996; Amato et al., 1997; Goldstein et al., 1996; Axelrod and Milner, 1997; Haley et al., 1997a,b; Haley and Kurt, 1997). In general, these studies have not found obvious and consistent changes in objective measures of numerous neurophysiological or neuropsychological variables; however, some of the studies have found subtle changes in several variables in some of the examined patients. Several hypotheses concerning the cause or physiological basis of difficult-to-diagnose chronic illnesses among some Gulf War veterans remain plausible; some investigators hypothesize relationships to stress (e.g., Goldstein et al., 1996; Amato et al. 1997), whereas other investigators hypothesize relationships to low-level chemical exposure (Haley and Kurt, 1997).

In an evaluation of neuromuscular function[18], Jamal et al. (1996) found statistically significant changes in two variables of nerve conduction velocity[19] and one variable of cold sensation in fourteen symptomatic[20] British Gulf War veterans compared with ten healthy civilians, but noted that the clinical relevance of these findings was unknown.

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[18] The evaluation included a physical examination of reflexes, muscle power, and response to stimulation (e.g., pin prick), nerve conduction velocity tests, electromyographic analysis of muscles, and quantitation of sensory thresholds to heat and vibration. 14 subjects (12 men and 2 women) were randomly selected by Jamal et al. from a list, compiled by a voluntary organization, of 40 U.K. veterans who complained of unexplained illness after the Gulf War.

[19] Among 19 nerve conduction and electrophysiological variables that were measured.

[20] These veterans reported musculoskeletal symptoms including fatigue, weakness, numbness and spontaneous sensations of heat or cold.

In evaluations of neuromuscular function and muscular structure[21] in 20 Gulf War veterans who complained of severe and debilitating muscle fatigue, weakness, or pain, Amato et al. (1997) reported that the only abnormalities[22] found were "mildly increased" levels of serum creatinine kinase or non-specific histological changes in biopsied muscle tissue in 8/20 of the patients. Amato et al. (1997) did not believe these changes to be clinically significant or indicative of a specific neuromuscular disorder.

Axelrod and Milner (1997) administered 36 neuropsychological tests to a group of 44 self-selected U.S. Gulf War veterans[23] and found that average performances for the group only showed slight, but statistically significant, impairments, relative to normal values, in two of six tests of finger dexterity and in three of twelve tests of executive functioning[24].

Goldstein et al. (1996) compared performance by 21 symptomatic Gulf War veterans and 38 healthy civilian volunteers in a battery of neuropsychological tests[25], and reported that no statistically significant differences were found between the two groups on scores in fourteen tests of cognitive processes (i.e., attention and memory). No statistically significant difference was found between the Gulf War veterans and the control group in a cognitive impairment index[26], when adjustment for psychological distress was made (Goldstein et al., 1996).

Using a mathematical technique, principal factor analysis, to identify associations among symptoms reported by a group of 249 Gulf War veterans, Haley et al. (1997a) identified and named six possible syndromes and studied subjects with the three syndromes showing the strongest associations among symptoms: *impaired cognition* (associated with: attention,

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[21] The evaluation included physical examination, determinations of serum creatine kinase and erythrocyte sedimentation rate, thyroid function tests, nerve conduction velocity tests, repetitive nerve stimulation tests, electromyographical analysis of several muscle groups, and microscopic examination of biopsied muscle tissue.

[22] Amato et al. (1997) noted that the frequencies of abnormalities which they observed in their group of 20 patients were less than that seen in other larger studies in which patients were referred for in-depth evaluation of muscle pain.

[23] This group of veterans reported experiencing joint pain (65%), skin rashes (57%), fatigue (57%), sleep disturbances (50%), shortness of breath (41%), and cognitive difficulties (39%).

[24] The three executive function tests with lower scores involved color naming and word naming. The other executive functioning tests administered included Trail Making tests, card-sorting tests, oral word association tests, and a test of semantic fluency.

[25] Included were tests of attention, memory, psychomotor function, and problem solving.

[26] The impairment index was based on the number of tests performed by a subject in which the score was below one standard deviation of the mean of the control group.

memory, and reasoning problems; insomnia; depression; daytime sleepiness; and headaches), *confusion-ataxia* (associated with: thinking problems; disorientation; balance disturbances; vertigo; and impotence), and *anthro-myo-neuropathy* (associated with: joint and muscle pain; muscle fatigue; difficulty lifting; and extremity paresthesias). In 23 symptomatic "cases" with these syndromes and 20 controls[27], Haley (1997b) examined performance in a battery of neuropsychological tests, auditory and vestibular function variables, brain stem auditory evoked potentials, somatosensory and visual evoked potentials, clinical motor and reflex functions, brain images, and numerous blood cytological and biochemical variables (see Appendix C for more details on administered tests and results). The following statistically significant differences between cases and controls were found: 6/22 cases showed weakness of the lower extremities compared with 1/20 controls; mean scores on composite indices of neuropsychological dysfunction were higher in cases than controls; and 4/23 cases versus 0/20 controls showed abnormal spontaneous nystagmus (rhythmic movement of the eyeball). In addition, mean values of several auditory and vestibular function variables[28] and several variables associated with evoked potentials[29] were significantly different (in the direction of impairment) in cases compared with controls.

The clinical significance of these differences is uncertain. Six neurologists, who were blinded to the identity of the subjects, reviewed the findings on each individual and concluded that "the clinical and laboratory findings were nonspecific and not sufficient to diagnose any known syndrome in any subgroup of the subjects." Haley et al. (1997b) speculated that the observed statistically significant differences between cases and controls in several objective measures of neurophysiological and audiovestibular variables may have a relationship with "sublethal exposures to cholinesterase-inhibiting chemicals", and noted that additional research is necessary, including examining the same, and additional, endpoints (e.g., neuromuscular and nerve conduction velocity variables) in a greater number of subjects (cases and controls).

Haley and Kurt (1997) hypothesized that the three previously discussed factor analysis-derived syndromes may represent variants of organophosphate-induced delayed peripheral neuropathy due to exposure to mixtures of anti-cholinesterase agents (e.g., chemical warfare nerve agents, pesticides, insect repellent, and/or pyridostigmine bromide). In support of this hypothesis, several statistically significant associations were found between self-reported exposures to anti-cholinesterase agents and the syndromes (e.g., wearing of pet flea and tick collars and *impaired cognition*; adverse reactions to pyridostigmine bromide and *confusion-ataxia* or *arthro-myo-*

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[27] Cases included 5 subjects with *impaired cognition*, 5 with *arthro-myo-neuropathy*, and 13 with *confusion-ataxia*. Controls, matched for age, sex, and educational level, included 10 deployed asymptomatic veterans and 10 non-deployed veterans. See Appendix C for more details.

[28] For example, increased interocular asymmetry in response to rotation.

[29] For example, increased latency of the lumbar-to-cerebral peaks on the posterior tibial somatosensory evoked potential.

neuropathy. See Appendix C for more details.) Landrigan (1997) has noted that the hypothesis put forth by Haley and colleagues is important and deserves serious investigation, but limitations[30] in the studies conducted to date "substantially weaken the authors' strong conclusions."

Several ongoing research projects are making efforts to identify specific physical or laboratory neurological variables that may be consistently affected in Gulf War veterans who are experiencing multiple chronic symptoms such as fatigue, headaches, and difficulty concentrating.

- At the University of Texas Southwestern Medical Center (DoD research project #65; RWG, 1998, 1999), a battery of clinical and laboratory tests are being developed to assess neurological variables that may be differentially affected in subjects with unexplained, multiple chronic symptoms compared with healthy subjects (e.g., regional cerebral blood flow before and after challenge with a carbamate cholinesterase inhibitor, nerve firing rate of peroneal nerve, quantitative electroencephalographic pattern analysis, and blood levels of serum butyrylcholinesterase). This group is also developing a plan to conduct another health and exposure survey of randomly selected national samples of deployed and non-deployed Gulf War-era veterans.

- At Georgetown University (DoD research project #31; RWG, 1998, 1999), several physiological variables (pain threshold, esophageal smooth muscle motility) and biochemical variables (changes in neurohormonal levels in response to different stressors, cerebral spinal fluid levels of neurotransmitters) are being examined in groups of ill Gulf-deployed veterans compared with groups of civilians experiencing similar multiple chronic symptoms and groups of healthy subjects.

- At Boston University, brain activation patterns (determined with magnetic resonance imaging) will be examined in groups of ill and healthy Gulf War-deployed U.S. veterans, a group of Germany-deployed veterans of the Gulf War era, and a group of ill, non-Gulf War deployed veterans (DHHS research project #5; RWG, 1999). Brain activation patterns will be assessed in subjects challenged with a test of working memory, a brain function thought to be affected in various disorders such as chronic fatigue syndrome, multiple chemical sensitivity, and post-traumatic stress disorder. This project will also administer neuropsychological tests to two groups of Danish veterans. One group was deployed to the Persian Gulf region in 1991 after the ground war ceased, and the other was not deployed to the Gulf.

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[30] Landrigan (1997) noted that the studies are focused on a single battalion of naval construction workers whose Gulf War experiences may not be representative of most Gulf War veterans; that only 41% of the battalion participated in the examinations raising the possibility of selection bias; that most information collected on illnesses was self-reported - detailed clinical and neuropsychological examinations were performed on only 23 symptomatic veterans representing less than 4% of the battalion; that motor nerve conduction velocity tests to confirm organophosphate-induced delayed peripheral neuropathy were made on only 5 veterans; and that exposure information was entirely self-reported.

Studies of Neurological Effects from Mixtures of Chemicals and other Risk Factors

As discussed in the previous section, there is limited suggestive evidence for the hypothesis that some Gulf War veterans with chronic, non-specific symptoms may be experiencing neurological dysfunction due to low-level exposures to mixtures of anti-cholinesterase agents that might have additive or synergistic effects (Haley et al., 1997a,b; Haley and Kurt, 1997).

Suggestive evidence of additive or synergistic effects among anti-cholinesterase agents is provided by three animal studies of acute (i.e., short-term) exposure: one with hens exposed to the anti-nerve agent, pyridostigmine bromide, the insect repellent, DEET, and the insecticide, permethrin, alone and in various combinations with each other (Abou-Donia et al., 1996a)[31]; another with hens exposed to pyridostigmine bromide, DEET, and the insecticide, chlorpyrifos, alone and in combination[32] (Abou-Donia et al., 1996b); and a third with rats given single doses of pyridostigmine bromide, DEET, and permethrin, alone and in various combinations[33] (McCain et al., 1997). The rat study found a significant increase in lethality when all three compounds were given compared with expected additive values based on lethality from exposure to the individual compounds; these findings suggest that the compounds interacted in a synergistic (greater than additive) manner (McCain et al., 1997). In the hen studies, individual compounds were administered at exposure levels that produced mild signs of neurological effects (e.g., transient leg weakness or diarrhea) and no, or minimal, microscopic changes in spinal cords or sciatic nerves (Abou-Donia et al., 1996a,b). Co-exposure to various combinations of two of the compounds produced signs of greater neurotoxicity (e.g., gait disturbances, tremors) and mild to moderate microscopic changes in the spinal cord and sciatic nerve of some of the hens; co-exposure to all three compounds produced marked neurotoxic signs and mild to severe changes in spinal cords and sciatic nerves (Abou-Donia et al., 1996a,b). Although the design of the hen studies does not allow definitive conclusions about synergistic interactions, the results suggest that additive effects occurred. The physiological or biochemical basis of these interactions is not

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[31] Hens were exposed 5 days/week for 2 months to oral doses of 5 mg/kg-day pyridostigmine bromide, subcutaneous doses of 500 mg/kg-day DEET, and subcutaneous doses of 50 mg/kg-day permethrin, alone, in binary combination, or all three together. Although the individual doses of these compounds did not produce marked neurotoxic effects in the hens, they were higher than doses experienced by Gulf War soldiers; for example, the prescribed dose of pyridostigmine bromide of 30 mg per 8 hours corresponds to about 1.3 mg/kg-day for a 70-kg subject.

[32] Hens were exposed 5 days/week for 2 months to oral doses of 5 mg/kg-day pyridostigmine bromide, subcutaneous doses of 500 mg/kg-day DEET, and subcutaneous doses of 10 mg/kg-day chlorpyrifos, alone, in binary combination, or all three together.

[33] Rats were exposed to several oral doses of each compound alone to determine acute oral lethal dose-response relationships. Interaction studies were then conducted examining lethality that occurred when low-level exposure to two of the compounds was constant and the dosages of the third compound were varied.

understood, but Abou-Donia et al. (1996a,b) hypothesized that competition among the compounds for esterases in the liver and plasma may lead to impaired breakdown and subsequent increased concentrations in nervous tissues[34].

The relevance of these animal studies to possible chronic neurological impairment in Gulf War veterans is uncertain due to the high exposure levels to which the animals were exposed[35], differences in routes of administration, potential physiological differences between humans and the studied animals, and other potential differences between mixtures to which the animals were exposed and mixtures that may have been experienced by Gulf War veterans (e.g., use of insecticides and insect repellents may have been low in the winter of 1991 when the use of pyridostigmine bromide occurred).

Acute exposure to some cholinesterase-inhibiting agents, such as certain organophosphate and carbamate insecticides, at exposure levels that produce acute symptoms of poisoning[36] is documented to produce different types of delayed or chronic neurological effects including persistent performance deficits on neuropsychological tests (Rosenstock et al., 1991; Ecobichon, 1994a,b; Steenland et al., 1994). Recent studies of subjects who experienced acute sarin poisoning in the Tokyo, Japan subway incident provide additional evidence that persistent subtle neurological deficits or changes may occur following acute high-level poisoning from cholinesterase-inhibiting chemicals (Murata et al., 1997; Yokoyama et al., 1998a,b). However, there are fewer data concerning persistent or long-term neurological effects from acute low-level exposures to cholinesterase inhibiting agents. Mice exposed to air concentrations of the organophosphate nerve agent, sarin, that did not produce obvious acute signs or symptoms of neurological damage[37] developed signs of peripheral neuropathy after exposure ceased, suggesting that obvious acute symptoms may not be a requirement for later developing neurological effects (Husain et al., 1993). Another study measured impairment in spatial learning in rats throughout a 21-day period following a 14-day treatment period with a potent organophosphate cholinesterase inhibitor at a dose that did not produce obvious signs of neurotoxicity (Prendergast et al., 1997).[38]

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[34] Buchholz et al. (1997) reported that co-exposure of rats to pyridostigmine bromide and permethrin caused a 30% decrease in nervous tissue doses of permethrin compared with permethrin exposure alone, and concluded that their results do not support Abou-Donia's proposed mechanism.

[35] McCain et al. (1997) noted that to achieve the lowest doses used in the rat study, a person weighing 70 kg would have to simultaneously ingest 107 30-mg pyridostigmine bromide tablets, 23 six-ounce aerosol cans of 0.5% permethrin, and 6.6 two-ounce tubes of 33% DEET.

[36] Acute symptoms can include increased secretions, tremors, and mental confusion due to stimulation of cholinergic nerves in the central and peripheral nervous system.

[37] 5 mg/m^3, 20 minutes/day for 10 days.

[38] Rats were given subcutaneous injections of 0, 50, 250, or 500 µg diisopropylfluorophosphate/ kg per day for 14 days (Prendergast et al., 1997). Diisopropylfluorophosphate is a potent organophosphate

In contrast, a recent study found no symptoms of neurological effects in a group of rescue workers, one year after they were involved in a sarin incident in Matsumoto, Japan without experiencing acute symptoms of neurological effects (Nakajima et al., 1997).

Animal studies have indicated that physically-induced stress may disrupt the blood-brain barrier (Sharma et al., 1991; Friedman et al., 1996), thus leading to the hypothesis that war-related stress may have facilitated increased nervous system concentrations of pyridostigmine bromide and caused adverse acute neurological reactions that would not have occurred under non-stress conditions. In support of this hypothesis, Friedman et al. (1996) reported that, after mice were subjected to a stress-inducing forced-swim protocol, the dose of pyridostigmine bromide that was required to inhibit brain acetyl cholinesterase activity by 50% was reduced to less than 0.01 of the usual dose under non-stress conditions. Friedman et al. (1996) suggested that this hypothesis may partially explain the findings that acute symptoms of central nervous system dysfunction[39] were reported by more than 23% of 213 soldiers who took pyridostigmine under wartime conditions and were surveyed within 24 hours, whereas in a double-blind, placebo-controlled study under non-stressed conditions, about 8% of subjects given the same dose of pyridostigmine bromide reported similar acute symptoms. Whether or not stress-induced acute effects on the blood-brain barrier are related to subtle neurological changes observed in some Gulf War veterans with chronic non-specific symptoms of ill health remains unknown.

Numerous animal studies relevant to interactions between various neurotoxic Gulf War chemicals and other risk factors (such as stress and botulinum toxoid vaccination) are in progress or are being prepared for publication.[40] Given the extensiveness of this research effort, it appears that

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inhibitor of acetylcholine esterase. The highest dose produced obvious signs of neurotoxicity (slowed movement, ataxia) that were not observed at the lower doses; at the two lower doses, subtle changes in behavior were noted during treatment. In rats from the two lower dose groups, cognitive function was assessed in a test of spatial learning at several intervals up to 21 days after treatment ceased; performance was impaired in rats treated with 250 µg/kg, but not in 50-µg/kg rats.

[39] Headaches, insomnia, drowsiness, nervousness, difficulties in focusing attention.

[40] These projects include: an examination of neurobehavioral variables in rats exposed to jet fuel vapor alone and in various combinations with insect repellent (DEET), pyridostigmine bromide, and periodic electric shock to induce stress (DoD research project #2; RWG, 1999); evaluation of neurobehavior and immune function variables in rats exposed to pyridostigmine bromide, permethrin, and DEET, alone or in combination (DoD research project #37; RWG, 1999); examination of possible delayed neurobehavioral and neuropathological effects in rats or monkeys following exposure to various cholinesterase inhibiting chemicals, alone or in various combinations or in combination with the administration of botulinum toxoid (DoD research projects # 54 and 61; RWG, 1999); examination of possible delayed respiratory and nervous system effects in guinea pigs and marmosets exposed to low-levels of sarin, with or without pretreatment with pyridostigmine (DoD research project #55; RWG, 1999); examination of possible delayed effects on neuromuscular and sensory systems in mice and hens exposed to low levels of sarin alone or in combination with pyridostigmine bromide (DoD research project #56; RWG,

additional animal studies currently are not needed, at least until research results from the ongoing studies can be evaluated.

Genetic Differences in Susceptibility to Environmental Agents

The Gulf War experience with and the clinical trials of the use of pyridostigmine bromide at the recommended dosage rate of 30 mg per 8 hours indicate that variable percentages of individuals experience acute symptoms of acetylcholinesterase inhibition including eye pain and headache, dizziness, runny nose, tightness in the chest, nausea, and/or abdominal cramps (Taylor, 1996; Keeler et al., 1991; Friedman et al., 1996). Keeler et al. (1991) reported that, during wartime use at this dose, the incidence of such "side effects" was around 1% and that about 0.1% of subjects experienced sufficiently severe effects to discontinue its use. Friedman et al. (1996) reported that in double-blind clinical trials with 35 healthy volunteers about 8% experienced acute symptoms of central nervous system dysfunction (e.g., headaches, insomnia, drowsiness, nervousness) and that, in studies with 213 soldiers under war-time conditions, similar symptoms were reported by about 24% of the subjects. In another report of the same study of 213 soldiers, Sharabi et al. (1991) noted that most individuals who experienced symptoms reported them as mild, but small percentages (3-10%) of subjects reported symptoms to be severe.

The underlying physiological, biochemical and/or genetic basis of why some individuals experience "side effects" from this pyridostigmine dosage rate is not understood and could vary from individual to individual. One hypothesis that is receiving some research attention is that differences among individuals in the level or the genotype of the blood serum enzyme, butyrylcholinesterase, may be responsible, at least in part, for differences among individuals in susceptiblility to acute effects from nerve agents that inhibit cholinesterases. Butyrylcholinesterase is thought to provide a normal protective mechanism whereby nerve agents, including pyridostigmine and organophosphate nerve agents, are "scavenged" and detoxified by chemical interaction with the enzyme. In support of this hypothesis, Loewenstein-Lichtenstein et al. (1995) reported that an Israeli soldier, who had experienced severe acute symptoms after taking pyridostigmine during the Gulf War, was found to have an 'atypical' butyrylcholinesterase that had a low potential to interact with pyridostigmine. Other support comes from animal experiments showing that the intravenous administration of acetylcholinesterase from fetal bovine serum or butyrylcholinesterase from human serum allows animals to survive, without toxic effects or neurobehavioral deficits, short-term exposures to a variety of organophosphate nerve agents at levels well above those that are normally lethal (see Wolfe et al., 1992).

It is unknown if individuals who have low levels of serum butyrylcholinesterase or who have 'atypical' butyrylcholinesterase will experience, after acute exposure to pyridostigmine or other nerve agents, delayed neurological impairments that are not experienced by others with normal

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1999); and examination of effects of low-level sarin, physical exercise, and pyridostigmine bromide on neurobehavioral, neurobiochemical, and neurophysiological variables in mice (DoD research project #62; RWG, 1999).

levels of typical butyrylcholinesterase. An ongoing exploratory research program at the University of Nebraska Medical Center (DoD research project #60, RWG, 1999) is comparing serum levels and genotypes of butyrylcholinesterase in healthy Gulf War veterans and Gulf War veterans who report chronic symptoms of ill health to determine if there are correlations between butyrylcholinesterase levels or genotype and generic chronic health symptoms associated with Gulf War service. A related ongoing project at the East Orange VA Medical Center is comparing neurobehavioral, physiological and biochemical responses to pyridostigmine, alone or in combination with physically-induced stress, in two strains of rats that differ in inherent serum levels of butyrylcholinesterase (DVA research project #49; RWG, 1999). This project is also examining if the amount of pyridostigmine that reaches the brain is different in the two strains of rats under conditions of repeated physically-induced stress compared with non-stress conditions.

In another ongoing exploratory program (DoD research project #51; RWG, 1999), a group at the Hebrew University of Jerusalem is genetically engineering mice to overexpress various types of cholinesterases in nervous tissue in an effort to understand genetic differences in susceptibility to nerve agents and to identify particular cholinesterase genotypes with the greatest potential to protect against acute toxicity from organophosphate nerve agents. In addition, this group is examining DNA from human subjects who display hypersensitivity to anti-cholinesterase agents, such as pyridostigmine, organophosphate insecticides, and organophosphate warfare nerve agents, in search of particular gene sequences that may correlate with hypersensitivity.

Multiple Chemical Sensitivity in Gulf War Veterans

Multiple chemical sensitivity is a hard-to-characterize disorder occurring in a subset of the general population in which individuals typically report a wide array of recurrent symptoms of ill health in response to very low concentrations of chemicals in the environment. Symptoms reported include fatigue, depression, headaches, gastrointestinal problems, muscle and joint pain, irritability, and memory and concentration difficulties (Miller, 1994). The biomedical community has not agreed on a case definition for this disorder due to several difficulties including the unreliability of self-reported symptoms linking illness to chemical exposure, the diversity of reported symptoms and their overlap with other illness such as chronic fatigue syndrome, post-traumatic stress disorder, and fibromyalgia, and the lack of a widely agreed upon diagnostic physical finding or test (Sorg et al., 1998; Bell et al., 1998a). The disorder has been proposed to occur following either long-term, low-level exposure or short-term, high-level exposure to chemicals. The underlying physiological basis of the disorder is not known, but several psychological, immunological, and biochemical mechanisms have been proposed (Miller, 1992, 1994; Buchwald and Garrity, 1994; Sorg, 1998; Bell et al., 1998a).

Fiedler et al. (1996) hypothesized that exposure to one or a combination of environmental agents during Gulf War service may be a contributing factor to health complaints in veterans with unexplained illnesses and that there may be a higher than expected prevalence of chronic fatigue syndrome and multiple chemical sensitivities among Gulf War veterans. Leading to this hypothesis was the observation that the most frequently reported symptoms among Gulf War

veterans with unexplained or undiagnosed illnesses in the DoD and DVA clinical programs[41] overlap with several of the required symptoms in the Center For Disease Control and Prevention's definition of chronic fatigue syndrome (fatigue, muscle/joint pain, headaches, and loss of memory; Fukuda et al., 1994), and are common in patients with multiple chemical sensitivities (Buchwald and Garrity, 1994).

A considerable prevalence of self-reported fatiguing illness and chemical sensitivities was found in a preliminary study that administered a questionnaire to a group of 432 Gulf War veterans who registered in the DVA Persian Gulf Health Registry; 203 previously listed fatigue as a medical complaint and 228 did not (Fiedler et al., 1996). Among those who initially reported fatigue and responded to the questionnaire: 89% reported that the fatiguing illness began in 1991 or 1992; 7% reported adopting three or more avoidance behaviors based on chemical sensitivities[42]; and 33% and 20% considered themselves especially sensitive to car exhaust and perfume, respectively. Among respondents who did not initially report fatigue, 63% reported developing fatiguing illness and 30% considered themselves sensitive to certain chemicals with 19% sensitive to car exhaust and 11% to perfume. A more extensive survey of 2800 registrants in the DVA Persian Gulf Health Registry is being conducted by this research group (DVA research project #5A; RWG, 1999). Ongoing analyses of these data (which include self-reported environmental exposures to chemicals) are examining potential associations among symptoms to define one or more case definitions of Gulf War unexplained illnesses and potential associations between environmental risk factors and symptoms.

In a small-scale telephone survey study, a statistically significant increased percentage of subjects who considered themselves especially sensitive to certain chemicals was found in ill Gulf-deployed veterans (12/14 subjects or 86%) compared with healthy Gulf-deployed veterans (3/10 or 30%), but not in ill non-deployed veterans (4/7 or 57%) compared with healthy non-deployed veterans (3/10 or 30%) (Bell et al. 1998b).

Although these studies (Fiedler et al., 1996; Bell et al., 1998b) suggest that chronic fatigue and chemical sensitivities are present among Gulf War veterans, they do not quantify the prevalence of these conditions among all Gulf War veterans because either the studied subjects do not represent a suitably large random sample of U.S. Gulf War veterans (both studies) or a control (non-deployed) group is not included. The importance of a control group to assess whether there is an increased prevalence of chemical sensitivities among Gulf War veterans is emphasized by results of past questionnaire studies of self-reported chemical sensitivity in other groups of people[43]

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[41] Fatigue, headache, memory problems, sleep disturbances, skin rash, joint pain, and shortness of breath.

[42] For example, following a special diet, wearing special clothes, taking special precautions in selecting home furnishings because of chemical sensitivities.

[43] Including college students, a rural population, office workers, and elderly WWII veterans.

showing that approximately 30% of subjects responded positively when questioned if they have chemical sensitivity and that only about 4-6% report chemical sensitivities severe enough to prompt drastic changes in their lifestyle (see Bell et al., 1998a,b). Although a larger scale study with a suitable questionnaire given to larger numbers of subjects representing random samples of all Gulf War veterans and non-deployed veterans from the same era may provide better information concerning prevalence of multiple chemical sensitivity, the lack of understanding of the neuropsychological and physiological basis of the condition itself may represent a more important problem to address with more research.

Research efforts to better understand physiological and neuropsychological characteristics in veterans reporting chronic fatigue and chemical sensitivities are ongoing at the East Orange, Tucson, and Boston VA Medical Centers, at Georgetown University (in collaboration with the Washington VA Medical Center), and at the University of Medicine and Dentistry of New Jersey. In general, it is believed that this research may lead to a better basis for proposing new methods of diagnosis and treatment of Gulf War veterans with unexplained chronic symptoms including chemical sensitivity.

- At the East Orange Center, healthy veterans and veterans with chronic fatigue and/or chemical sensitivities have received comprehensive medical evaluations[44] and the results are being compared with civilians with chronic fatigue syndrome and/or chemical sensitivities (DVA research project #5B; RWG, 1999). A related research project is ongoing in which the effects[45] of short-term exposure to 5 ppm diesel exhaust and aerobic exercise are being compared in healthy veterans and veterans with chronic fatigue syndrome and/or chemical sensitivities (DVA research project #5C; RWG, 1998, 1999).
- At the Tucson Center, several physiological and neuropsychological variables[46] will be measured in several groups of veterans following repeated exposure to controlled concentrations of jet fuel vapor or air (DVA research project #48; RWG, 1999). Subjects will include groups of ill Gulf War veterans with or without chemical sensitivity, healthy Gulf War veterans without chemical sensitivity, and healthy, non-deployed veterans of the Gulf War era.

- At the Boston Center, in-depth neuropsychological evaluations that will diagnose multiple chemical sensitivity, chronic fatigue syndrome, post-traumatic stress disorder, and other related disorders have been given to groups of treatment-seeking Gulf War veterans and

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[44] Included were evaluations for viral infections and immune dysfunction, tests of neuropsychological variables, and tests of physiological responses to physical and cognitive challenges.

[45] Endpoints evaluated include self-reported symptoms, physiological responses such as heart rate and blood pressure, and performance in tests of cognitive ability.

[46] Endpoints will include blood pressure, heart rate, eyeblink and performance in tests of cognitive ability.

non-deployed veterans and groups of non-treatment seeking veterans (DoD research project #32; RWG, 1999). Analysis of collected data for over 300 subjects is ongoing and expected to have the potential to reveal differences between treatment-seeking deployed and non-deployed Gulf War-era veterans. A short questionnaire to identify multiple chemical sensitivity also has been developed (DoD research project #52; RWG, 1999). This will be used to compare prevalence of chemical sensitivities in female and male members of a cohort of Gulf War veterans and explore risk factors for the development of this condition.

- At Georgetown University (in collaboration with the Washington VA Center), physiologic and biochemical variables[47] have been measured in Gulf War veterans with unexplained chronic symptoms, in civilian patients with chronic fatigue syndrome or fibromyalgia, and in healthy controls (DoD research project #31; RWG, 1999).

- At the University of Medicine and Dentistry of New Jersey, the persistence of self-reported symptoms over time will be evaluated in a group of Gulf War veterans (DHHS research project #6; RWG, 1999). In addition, working definitions for multiple symptom illnesses, such as chronic fatigue syndrome and multiple chemical sensitivity, will be compared with alternative definitions as descriptors of unexplained illnesses in Gulf War veterans.

Treatment of Gulf War Veterans with Non-specific Chronic Symptoms of Ill Health

The DoD's Gulf War Health Center has a *Specialized Care Program* for people with persistent, non-specific symptoms associated with Gulf War service (Engel et al., 1998). This program is a 3-week outpatient treatment program involving three multidisciplinary teams of caregivers: a medical team, a physical team, and a psychosocial team. The program involves medical evaluations, exercise programs, therapy programs (e.g., physical, occupational, and recreational), and counseling. Patients are referred to this program after being evaluated in the DoD's Comprehensive Clinical Evaluation Program. A meta-analysis of studies of these types of programs for patients with chronic pain suggests they are useful in improving pain and mood, facilitating returning to work, and decreasing utilization of health care systems (Flor et al., 1992).

The DVA and DoD have established a 2-year, multiple-site, randomized control trial (starting in 1999 and ending in 2001) to compare treatment methods for U.S. Gulf War veterans who have unexplained chronic symptoms of pain, fatigue, and/or cognitive difficulties (DVA/DoD research project # 1D & 1V; RWG, 1999). Patients will be Gulf War veterans who are chronically experiencing at least two of the following self-reported symptoms: 1) fatigue that limits work, recreational, or social activity; 2) musculoskeletal pain in two or more body regions; and 3)

[47] Variables include qualitative measures of general health symptoms, quantitative measures of pain and muscle motility, heart rate variability, levels of neurohormones in response to stress, and levels of neurotransmitters in cerebral spinal fluid.

difficulties in memory, concentration, or attention. The program will evaluate 339 randomly assigned patients in each of four treatment groups[48]: 1) "usual and customary care" (the control group); 2) cognitive behavioral therapy[49] plus usual and customary care; 3) aerobic exercise plus usual and customary care; and 4) cognitive behavioral therapy, plus aerobic exercise, and usual and customary care. Treatment will be in a group format and will last for 3 months (one hourly session per week for 12 weeks). Patients will be evaluated for physical function before and immediately after the end of treatment and at 6 and 12 months after start of treatment.

Limited research has investigated the possibility that some veterans with non-specific chronic symptoms may be infected with microorganisms that are difficult to detect and that treatment with antibiotics may be useful in alleviating symptoms (Nicolson and Nicolson, 1996; Nicolson et al., 1998; Nicolson, 1998; Hyman, 1996; See Appendix C for study details). Nicolson and Nicolson (1996) reported that mycoplasma gene sequences were detected in blood leukocytes from 14 subjects in a group of 30 Gulf War veterans with chronic symptoms similar to those associated with chronic fatigue syndrome and that 11/14 of these subjects recovered after multiple treatment cycles of antibiotics (doxycycline or ciprofloxacin). Nicolson et al. (1998) also reported that mycoplasma gene sequences were detected in blood leukocytes of 76 subjects in a group of 170 subjects comprised of Gulf War veterans with chronic-fatigue-syndrome-like symptoms and their immediate family members. Among 73 mycoplasma-positive subjects who received two to six 6-week cycles of antibiotic therapy (doxycycline, ciprofloxacin or azithromycin), 58 were reported to have recovered. Hyman (1996) reported detecting streptococcal bacteria remnants in urine of about ten Gulf War veterans who had chronic-fatigue-syndrome/fibromyalgia-like symptoms (and their immediate family members); treatment with antibiotics was reported to improve the health of the subjects initially, but most relapsed. Limitations of these studies include the lack of blind testing of the specimens, the lack of appropriate control groups, and the lack of investigation of a possible placebo effect (i.e., the lack of blinding of the subjects).

Further research is ongoing regarding the antibiotic treatment of Gulf War veterans with non-specific, chronic symptoms such as fatigue, difficulty concentrating, joint and muscle pain, and headache. The DVA has recently established a multiple-site, 30-month, double-blind clinical trial of antibiotic treatment of symptomatic patients with positive findings for mycoplasma infection (DVA research project # 55; RWG, 1999). The trial (to be conducted between 1999 and 2001) will identify 450 Gulf War veterans who are experiencing at least two of three chronic symptoms (fatigue, musculoskeletal pain, and neurocognitive dysfunction) and who are mycoplasma-positive. Subjects will be randomly assigned to 12-month treatments with either 300 mg

[48] A total of 1356 patients.

[49] Cognitive Behavioral Therapy is a set of techniques that are based on psychological principles of behavioral conditioning (e.g., positive and negative reinforcement) and observational learning and are administered, with active patient participation, by a clinician trained in behavioral medicine. These techniques have been used in the treatment of physical problems such as low back pain, headaches, fibromyalgia (muscle pain), chronic fatigue, asthma, and arthritis (RWG, 1999).

doxycycline per day or placebo. Patients will be seen monthly during the medication phase and at 18 months. Physical function will be evaluated before treatment starts, and at 3, 6, 9, 12 and 18 months. Patients will also complete questionnaires designed to provide measures of pain, fatigue, and neurocognitive dysfunction.

Another project, funded by the DoD and conducted by the Louisiana Medical Foundation, involves blinded and placebo-controlled clinical trials of antibiotic treatment of patients who are experiencing chronic non-specific symptoms and who show bacterial remnants in their urine (DoD research project # 67; RWG, 1998; 1999). This trial is expected to be completed in 1999.

6. Concluding Remarks

During the upcoming two-and-a-half day conference, participants from various disciplines will meet several times in workgroups with the goal of discussing and recommending research in one of four focus areas related to illnesses among Gulf War veterans:

- Workgroup 1: Pathophysiology, Etiology, and Mechanisms of Action;
- Workgroup 2: Assessment/Diagnosis;
- Workgroup 3: Treatment; and
- Workgroup 4: Prevention.

A central question to be addressed by Workgroup 1 is: What are the most plausible etiological hypotheses concerning 1) diagnosed diseases and 2) unexplained multiple-symptom illnesses noted among Gulf War veterans? Associated questions include: Are ongoing research projects addressing the most plausible of these hypotheses? If not, which additional plausible hypotheses should be addressed? Are there research methods or approaches that need to be developed, or that are available and not being used? The Gulf War experience has created interest in the health effects of particular chemical agents, such as depleted uranium, organophosphate chemical warfare nerve agents, carbamate prophylatic agents against organophosphate nerve agents, vaccines, and organophosphate pesticides. This interest leads to additional questions within the focus of Workgroup 1. Should additional research resources be applied to better understand exposure-response relationships for, mechanisms of actions of, individual susceptibility to, and/or biomarkers of exposure to specific chemical agents or classes of agents associated with the Gulf War experience? Are current research efforts to examine potential interactions among "Gulf war mixtures" of chemicals and other health risk factors of sufficient scope and design? What alternative research approaches could be taken to decrease the uncertainty that will exist in any future attempts to extrapolate results from the animal "mixtures" experiments to expected human exposure scenarios? Should such research efforts be made?

Results from several epidemiological studies concur that Gulf War veterans more frequently report multiple symptoms of ill health than non-deployed veterans of the same era and that there may be an increased frequency of chronic, multi-systemic conditions of ill health among groups of Gulf War veterans. The array of reported symptoms are, in general, difficult to diagnose into a disease category. The most frequently reported chronic symptoms among Gulf War veterans with