The 1990-91 Gulf War

The 1990-91 Persian Gulf War was an international conflict in response to Iraq’s invasion and annexation of Kuwait. In anticipation of a conflict to liberate Kuwait, the United States and an allied Coalition of 34 nations initiated a military buildup code-named Operation Desert Shield. That Coalition included the United States, United Kingdom, France, Saudi Arabia, and other nations. The buildup was begun in August 1990 and continued through January 1991, at which time Coalition troops at the ready included 700,000 U.S. personnel.

The Southwest Asia theater of operations is generally defined as the area that includes the Persian Gulf, Red Sea, Gulf of Oman, Gulf of Aden, and a portion of the Arabian Sea, as well as the total land areas of Iraq, Kuwait, Saudi Arabia, Oman, Bahrain, Qatar, and United Arab Emirates.

Coalition attacks on Iraqi forces began with a massive 6-week air and naval bombardment campaign on January 17, 1991, aimed at targets within Iraq. In response, Saddam Hussein launched missiles at targets within Israel, Saudi Arabia, Bahrain, and Qatar. This combat phase was code-named Operation Desert Storm.

The bombardment phase was followed by a ground assault on February 23, 1991. The ground assault was code-named Operation Desert Sabre, but it is often referred to as the second phase of Operation Desert Storm. U.S. troops engaged in heavy battles against the Iraqi forces, including fierce tank battles and breaching of minefields. As Coalition forces advanced into Kuwait, many of the remaining Iraqi troops positioned there surrendered to Coalition forces. Others set fire to 600-700 oil wells in Kuwait as they retreated into Iraq. Coalition forces also advanced into Iraq through the western frontier with Saudi Arabia, outflanking and encircling the retreating Iraqi military.

The outcome was a decisive victory for the Coalition forces. By the time that President George H.W. Bush declared a cease-fire to the Gulf War (GW) on February 28, 1991, most Iraqi forces in Kuwait had either surrendered or fled. By July 1991, the last U.S. troops who had participated in the ground war returned home. U.S. forces experienced 147 casualties on the battlefield, and an additional 145 personnel were killed by non-battle-related causes.

Gulf War Illness Primary Features, Prevalence and Prognosis

Symptoms of Gulf War Illness

Within a short time after the 1990-91 GW, Veterans who served in and around the theater of operations developed enduring chronic, unexplained conditions and/or constellations of symptoms and illnesses that could not be explained by established medical/psychiatric diagnoses or standard laboratory tests.
Symptoms experienced and reported by GW Veterans vary widely. However, the multitude of reported symptoms are of a similar clinical description and usually include combinations of widespread pain, muscle aches, headache, persistent problems with memory and thinking, fatigue, breathing problems, stomach and intestinal symptoms, and skin abnormalities. In addition to the physical issues involved, changes in behavior and problems with interpersonal relationships frequently occurred.

Initially, this constellation of disorders was referred to as “Gulf War Syndrome.” Other names given to these problems included chronic multi-symptom illness (CMI), undiagnosed illness, Gulf War Illness (GWI), and other terms. Currently, “Gulf War illness” is the term recommended by the National Academy of Medicine (formerly the Institute of Medicine [IOM]) and is most commonly used by scientists, clinicians, Veterans organizations, and the U.S. Department of Defense (DoD).

**Prevalence**

GWI is estimated to have affected 175,000 to 250,000 of the nearly 700,000 troops deployed to the 1990-91 GW theater of operations. Twenty-seven of the 28 Coalition members participating in the GW conflict have reported GWI in their troops. Epidemiologic studies indicate that rates of GWI vary in different subgroups of GW Veterans. GWI affects Veterans who served in the U.S. Army and Marines Corps at higher rates than those who served in the Navy and Air Force, and U.S. enlisted personnel are affected more than officers. Studies also indicate that GWI rates differ according to where Veterans were located during deployment, with the highest rates among troops who served in forward areas.

**Prognosis**

The 2014 report by the U.S. Department of Veterans Affairs (VA) Research Advisory Committee on Gulf War Veterans’ Illnesses (RAC) summarized investigations addressing health changes related to GWI (RACGWVI Research Update and Recommendations, 2004). The report states that Veterans of the 1990-91 GW generally are in poorer health and present with greater disability than other Veterans of the same era that were not deployed to the Persian Gulf. Research suggests that the GWI symptomology experienced by Veterans has not improved over the last 25 years, with few experiencing improvement or recovery.
Etiology of Gulf War Illness

During the GW, Service members were exposed to low levels of chemicals, including chemical warfare agents released by the destruction of Iraqi facilities, widespread spraying and use of pesticides, prophylactic medications to protect against hazardous exposures, constant dust and sand storms, and effluent from oil well fires ignited by Iraqi troops. Uncertainties regarding types and doses of agent exposures, as well as a lack of scientific knowledge about the synergistic effects of combined agent exposures, have precluded a consistent theory of GWI etiology.

GW-Relevant Exposures

Cholinergic agents represent the most likely class of compounds with the broadest exposures experienced by Service members deployed to the GW. Of these, the organophosphates comprising the chemical warfare agents sarin, cyclosarin, soman, and the pesticides permethrin (PER) and chlorpyrifos (CPF) have received considerable attention. Other cholinergic agents include pyridostigmine bromide (PB) pills, which were given as a prophylaxis against nerve agents, and the insect repellant N,N-diethyl-meta-toluamide (DEET). Virtually all deployed troops were exposed to the pesticide PER, which was used on clothing to kill insects, the area pesticide CPF, which was used in no-pest strips in mess and residential areas, and the insect repellent DEET, which was applied directly to skin. Many troops were given PB pills regularly in anticipation of a nerve agent attack, and many troops were likely exposed to vapor plumes resulting from destruction of chemical weapons, including sarin, cyclosarin, and possibly mustard gas and soman.

Exposures to other possible etiologic agents include airborne particulates and emissions from Kuwaiti oil well fires, desert dust, multiple vaccinations (including anthrax vaccination), depleted uranium (DU), chemical-resistant coating (CARC) paint, psychological and physiological stress, heat, and miscellaneous petroleum products such as cleaners, lubricants, and fuels. It is generally assumed that individuals meeting the criteria for GWI were likely exposed to multiple agents.

Other Etiologic Considerations

Genetics, epigenetics, and gene-environment interactions are being investigated for potentially contributing to GWI. Multiple studies have examined the role of Paraoxonase 1 (PON1, particularly the PON1_192 subtype) variability and its association with susceptibility for GWI. PON1 is responsible for the metabolism of organophosphates that are thought to be primary contributors to GWI (Haley, 1999). The combination of certain less common genotypes of the enzyme butyrylcholinesterase (BChE, another gene involved in organophosphate detoxification)
with pyridostigmine bromide use (common during the GW) was shown to confer greater risk for developing GWI (Steele, 2015). Studies are underway to assess DNA damage from GW exposures by measuring somatic mutation frequency, overall genome instability, and chronic alterations in global DNA methylation.

Traumatic brain injury (TBI) was not considered common in the 1990-91 GW. Therefore, the relationship between TBI and chronic health symptoms experienced by GW veterans is unknown. However, GW Veterans’ self-reported exposure to TBI has been shown to be related to increased rates of chronic health symptoms and chronic multi-symptom illness (Yee, 2016) (Yee, 2017).

**GW-Relevant Models**

Several animal models have been developed to elucidate possible molecular and physiological mechanisms underlying GWI. These models have been used to characterize molecular, cellular, and functional effects associated with chemical exposures similar to those encountered by Veterans during the GW. These studies have provided evidence for brain, autonomic, behavioral, neuroendocrine, immune, and epigenetic effects and support unique dysfunction in ill GW Veterans.

White, et al., summarized a number of rat and mouse studies evaluating the effects of exposures including combinations of PB, PER, CPF, sarin, diisopropyl fluorophosphates (DFP, a sarin surrogate), and stress. In many cases, exposures were administered at dosage levels that do not produce overt symptoms of toxicity (White, 2016 p. Section 5). Beginning with the work of Abou-Donia and colleagues with a rat model of PB, DEET, and CPF exposures (Abou-Donia, 1996), these models have been shown to recreate GWI-like symptoms. Furthermore, these studies have shown that absorption, metabolism, and biological functions following exposure to a combination of chemicals are different than the absorption, metabolism, and biological functions of the individual exposures when studied separately (RACGWVI Scientific Findings and Recommendations, 2008). The findings obtained with several rodent GWI models are described below; however, this is not a comprehensive list of GWI models. Further animal model development supported by the DoD Gulf War Illness Research Program (GWIRP) can be found at (http://cdmrp.army.mil/gwirp/resources/gwirresources.shtml).

Several investigators have exposed rodents to a combination of PB, PER, DEET, and restraint stress in doses that do not give rise to immediately apparent toxic effects. Such treatment was reported to result in depressive behavior, lack of motivation, and memory defects (Hattiangady, 2014; Parhar 2013); induce abnormal lipid metabolism and increase immune signaling (Abdullah, 2012); and induce long-term epigenetic alterations (Pierce, 2016). Other rodent models have shown various types of delayed central nervous system (CNS) abnormalities that appear sometime after exposures to combinations of CPF with DEET or PB or PB plus PER (Nutter, 2015; Cooper, 2016; Torres-Altoro, 2011; Ojo 2014).
Evidence of CNS inflammation was reported early on (Bozkurt, 2010) and recently has been the subject of extensive research. A series of studies has established a model based on dual exposure to PB and PER (Abou-Donia, 2004). Using this model, researchers have documented neurobehavioral, neuropathological, and neuroinflammatory effects after PB plus PER exposure in the short, mid-, and long term. Genomic and proteomic studies were used to discern many features of the neuroinflammatory effect (Abdullah, 2011 and 2013; Zarikova, 2015 and 2016).

O’Callaghan, et al., recently reported very compelling results using only a single chemical agent (O’Callaghan, 2015); however, this exposure was preceded by pretreatment with corticosterone (CORT), a stress hormone that would normally be expected to suppress inflammatory responses produced by external stressors. Exposure to a single dose of the acetylcholinesterase inhibitor DFP, a surrogate for the chemical warfare agent sarin, was found to result in inflammation in the brain, but pretreatment with CORT was found to exacerbate the CNS inflammatory response and produce a persistent “priming” of the immune system, continuing to generate exacerbated responses to subsequent irritant challenges. The priming was found to be maintained for months in the mouse model (equivalent of 20 years in humans) by periodic low dosing with CORT. This model has been expanded in research being carried out by two research consortia funded by the GWIRP to identify new features of GWI pathobiology and new targets for treatment (Morris, FY12; Sullivan, 2012). In 2017, O’Callaghan, et al., showed that the model’s neuroinflammatory effects do not appear related to the AChE inhibition induced by these organophosphate agents, but these exposures may exert their effects on the brain through the “organophosphorylation” of other neuroimmune targets (Locker, 2017).

Other studies have focused on additional cellular and subcellular targets of GW chemical agents and suggest abnormalities associated with cholinesterases, tubulin (Grigoryan, 2008 and 2009, Jiang, 2010), impaired axonal transport (Rao, 2017) and mitochondrial dysfunction (Middlemore-Risher, 2011). Microtubule dysfunction has also been investigated (Rao, 2017), and mitochondrial defects have been the target of experimental treatment approaches (Golomb, 2014).

GWIRP-funded investigators have generated induced pluripotent stem cell cultures from skin fibroblast cells from deployed GW Veterans who have GWI symptoms, as well as those who did not develop GWI. These cells are being made available to the research community with the intent to foster rapid-throughput studies of novel therapeutic approaches (Qiang, 2017).

Pathobiology of Gulf War Illness

Because exposures to various neurotoxicants were known to occur in the GW and many of the symptoms of GWI clearly relate to nervous system dysfunction, much GWI research has focused on pathobiology of the nervous system. Other areas that have been and are actively being investigated include the immune/inflammatory system,
gastrointestinal system, and molecular systems for respiration and management of oxidative potential. From studies that have included female GW Veterans, it appears that gender differences may play a role in the underlying pathobiology of GWI.

**Imaging Studies**

Consistent differences between GWI cases and controls have been demonstrated using various brain imaging technologies to measure brain structure and function.

Structural magnetic resonance imaging (MRI) techniques have been employed in GW Veteran populations to determine structural changes in the brain, such as a reduction in brain size due to specific exposures in theater or changes occurring after GWI diagnosis. MRI-based measurements of specific brain areas and their volumes (segmentation and volumetry techniques) have revealed frank reductions of white and gray matter volumes in Veterans with suspected sarin/cyclosarin-exposure when compared to controls (Chao 2010, 2011, and 2014). Using Diffusion Tensor Imaging, which assesses the integrity and connectivity of white matter structures to other parts of the brain, Rayhan and Stevens reported increased axial diffusivity in subjects with GWI compared to controls. These results suggest that the white matter in GWI patients functions less effectively. Furthermore, they reported that increased diffusivity seen in the GWI patients was associated with increased fatigue, pain, and hyperalgesia (Rayhan, 2013b). Chao, et al., also observed increased axial diffusivity in GWI patients and found that the increased diffusivity correlated with poorer neurobehavioral performance (Chao, 2015). In functional MRI (fMRI) studies, where activation of brain structures in response to cognitive and other behavioral challenges can be visualized, Calley, et al., reported case/control differences in specific brain regions during a Semantic Object Retrieval Test (Calley, 2010).

fMRI studies using a pre-/post-exercise protocol showed that brain regions activated in response to innocuous heat stimulus following exercise were different among Veterans diagnosed with the three subtypes of GWI defined by the Haley criteria (Haley, 2001) and that, as a whole, the GWI group had distinct responses post-exercise when compared to the control group (Gopinath, 2012). Furthermore, the Haley-defined GWI subgroups showed atrophy in different brain regions and exhibited compensation in different brain regions during a verbal working memory task following exercise. Another MRI study revealed case/control differences in regional brain activation during memory encoding and memory recall (Hubbard, 2013).

Brain functional patterns measured by magnetoencephalography showed that patterns of synchronous neural interactions (SNI) were distinctly different in those with GWI compared to healthy controls. Moreover, GWI-SNIs did not differ significantly from known immune-related diseases (rheumatoid arthritis, Sjogren’s syndrome), but did differ significantly from Alzheimer’s, schizophrenia, and post-traumatic stress disorder (PTSD) SNIs (Georgopoulos, 2017).

**Neurocognitive Findings**

Because the neurocognitive and affective symptoms reported by GW Veterans commonly include problems in memory, concentration, and mood, psychological tests are often used to quantify neurobehavioral function in this Veteran group.
A large study comparing deployed GW Veterans versus non-deployed GW-era Veterans found that deployed participants performed worse than their non-deployed counterparts on tests that assess short-term memory attention, visuospatial abilities, executive function, and fine motor coordination and speed (Toomey, 2009). Differences in performance on specific cognitive tasks were associated with self-reported exposures to specific chemical agents in theater. Self-reported exposure was found to predict poorer performance outcomes on measures of short-term memory, attention, and affective functions (White, 2001), as well as to be associated with poorer executive function and greater mood complaints (Sullivan, 2003). In a number of studies, researchers reported poorer visuospatial and memory functions and greater dysphoria in Veterans meeting the criteria for GWI versus controls (Anger, 1999; Axelrod, 1997; Binder, 1999; Bunegin, 2001; Lange, 2001; Storzbach 2000 and 2001; Odegard, 2013; Sullivan, 2003). One study showed little difference between cases and controls in cognitive domains, but did find significantly poorer reports of mood and quality of life in those with GWI (Wallin, 2009); this study involved a very small sample of GW-deployed Veterans and lacked the statistical power to detect subtle but significant differences in cognitive outcomes.

**Autonomic and Neuroendocrine Systems**

Studies have linked autonomic dysregulation to symptoms experienced by GW Veterans. In these studies, important differences in function among ill GW Veterans, controls, and Veterans with differing Haley syndromes are not apparent during resting or work, but rather emerge following some type of physiological challenge. The challenge used in these studies is most often physical exercise, but can take other forms. In animal models, pharmacological challenges have been used (e.g., drugs that increase heart rate). Studies in the GWI literature referring to pre- and post-challenge testing most often refer to testing before and after such a challenge (or during peak effort), but not to testing before and after chemical exposure, as is often the case in many toxicological studies.

Tests of parasympathetic and sympathetic nervous system regulation in GW Veterans have demonstrated that some symptoms, such as chronic diarrhea, dizziness, and fatigue, as well as changes in cardiovascular indices, may be due to subtle autonomic system dysfunction (Haley 2004; Rayhan, 2013a).

Due to the extreme conditions of deployment and possible exposure to pathogenic agents during the GW, it has been suggested that the neuroendocrine control system may have been pushed beyond its normal operating capacity. Thus, neuroendocrine dysregulation as a result of GW deployment has been reported, including demonstrations of pronounced differences between GWI Veterans and controls after exercise and other challenges. Specific patterns of altered hypothalamic-pituitary-adrenal (HPA) axis functioning that are distinct from other conditions such as PTSD have been identified (Ben-Zivi, 2009; Golier, 2007 and 2009). A GWIRP-funded project (Craddock, 2014) found that regulation of sex hormones through the hypothalamic-pituitary-gonad (HPG) axis and components of innate and adaptive immunity undergo distinct and significant remodeling following exercise challenges in Veterans with GWI (Broderick, 2011).

Further investigation into altered regulation of these systems is ongoing. Research under a GWIRP-supported consortium integrated basic and clinical research to identify the metabolic signaling mechanisms involved in disruption of autonomic cardiovascular function and
endocrine functions in GWI (Morris, FY 2012). Results to date suggest there are changes in cardiac regulation associated with GW-era exposure.

**Neuroimmune Response**

Evidence from various fields has demonstrated multiple channels of communication between the brain and the immune system, and brain-immune interrelationships have been investigated in GWI. In the short term, inflammatory responses generated by the immune system are helpful and elicit self-preserving physical responses; however, chronic inflammation can be maladaptive. This observation led to recent interest in neuroinflammatory chronic glial activation as a potential cause of chronic symptoms in GWI. Chronic glial activation results in the synthesis and release of pro-inflammatory cytokines and chemokines (O'Callaghan, 2008) and is particularly relevant to GWI because the effects are seen in both gray and white brain matter. Gray and white matter volumes have both been shown to be reduced in neurotoxicant-exposed and symptomatic GW Veterans (see Brain Imaging Studies above). In addition to lower white matter volumes, studies have shown reduced information processing speeds in symptomatic GW Veterans exposed to low-dose sarin, a neurotoxicant (Proctor, 2006). Taken together, the findings of reduced white matter volumes and poorer information processing suggest that glial cells may have an important role in the development of (and ongoing) health symptoms and the cognitive complaints of GW Veterans. A GWIRP-funded project (Klimas, FY 2008) used comprehensive molecular profiling, combined with control theory, to link a stress-potentiated neuro-inflammatory response with symptom severity and identified changes in immune cell abundance, function, and signaling (Broderick, 2013).

Further investigation into whether GWI is related to chronic brain-immune activation and inflammation is ongoing under a GWIRP-supported consortium (Sullivan, 2012). A pilot study conducted by this group showed that serum antibodies for a series of neuronal and glial-specific proteins (CaMKII, GFAP, tau, tubulin, MAG, MBP, NFP, and MAP-2) were significantly elevated in a GWI cohort. The results must be validated further, but they support continued study into glial signaling white matter alterations and brain neuronal degeneration. These findings may also contribute to development of a panel of objective biomarkers of GWI.

**Mitochondrial Dysfunction**

Exposures linked to GWI are known to impair cell energy, and adverse cell energetics have been shown to contribute to symptoms consistent with GWI. Given these observations and because the mitochondrion is the source of chemical energy for the cell, the potential relationship between mitochondrial dysfunction and GWI has been subject to investigation. A GWIRP-funded study recently provided the first objective evidence of mitochondrial dysfunction in Veterans with GWI. Compared to controls, Veterans with GWI exhibited prolonged post-exercise recovery of phosphocreatine, a compound used as a backup energy store and a robust index of mitochondrial function (Koslik, 2014). This finding supports the presence of mitochondrial pathology in GWI.

**Transport Impairment**

Tau pathology has been suggested as a potential contributor to GWI pathobiology, and has been subject to investigation. To date, GW-relevant organophosphate neurotoxicants have been shown to lead to significantly decreased microtubule width in neurons (Jiang, 2010).
Large-Scale Efforts and Resources

Large-scale genotype and phenotype efforts are planned and/or are underway through collaborative efforts at the VA and National Institutes of Health (NIH). These studies will examine relationships between genetic variations and the physical traits of ill GW Veterans.

A biorepository effort and published pathobiological biomarker studies supported by the GWIRP to date can be found at http://cdmrp.army.mil/gwirp/resources/gwirpresources.shtml. These efforts are expected to foster collaboration and serve as a significant resource for the research community.

Gulf War Illness Case Definitions

Research on GWI has relied on a number of differing definitions of the disorder, including CMI (Fukuda, 1998), the Kansas GWI definition (Steele, 2000), the Haley syndrome criteria (Haley, 1997 and 2001), and adaptations of these approaches. An IOM panel recommended the use of the CMI definition in clinical settings, as it is somewhat inclusive (IOM, 2014). In the same report, the panel also recommended use of the Kansas definition in research settings because it is more selective and includes various exclusionary criteria. Current best practice in research is to use of one of the two IOM-recommended case definitions (CMI or Kansas) for primary analyses that best fit the current study and also include the criteria that allow use of the other definition to facilitate cross-comparison of study results. For example, a study of GW populations might categorize participants primarily according to the Kansas definition, but further categorize them according to the CMI definition to allow comparisons to prior studies that have used that definition.

The CMI Definition (Also Known as the Fukuda or CDC Definition)

The CMI case definition was developed by the U.S. Centers for Disease Control and Prevention (CDC) and was derived from clinical data and statistical analyses (Fukuda, 1998). The investigators conducted a cross-sectional survey in a Pennsylvania-based Air National Guard unit and three comparison Air Force units.

The CMI definition is variously referred to in the literature by that name, as well as the CDC definition (after the primary author’s home institution) and the Fukuda definition (after the primary author). CMI is the most commonly used GWI case definition in epidemiologic research to date and is somewhat inclusive. In the primary publication describing the definition, the prevalence of GWI in deployed Veterans ran as high as 45% using the CMI criteria. The VA RAC estimated use of this definition to yield a prevalence as high as about 32% in the population of GW Veterans.

This symptom-category approach included a principal-components analysis of symptoms of fatigue, difficulty remembering or concentrating, moodiness, difficulty sleeping, and joint pain or stiffness, followed by a confirmatory factor analysis. The definition requires at least one chronic
(experienced longer than 6 months) symptom in at least two of three categories: fatigue, mood and cognition, and musculoskeletal. It also allows sub-classification by severity; cases are considered severe when at least one symptom in each of the required categories is rated as severe. Risk factors associated with CMI include deployment to the GW, rank, age, being female, and smoking. GWI cases in the study also reported reduced functioning.

The Kansas Definition

The name “Kansas definition” reflects the origin of the Veteran group participating in the study that formulated the criteria for this definition of GWI. In the primary publication describing the definition, the prevalence of GWI in deployed Veterans ran as high as 34%. The VA RACGWVI estimated that using the Kansas criteria to define GWI yields a prevalence in the range of 25% in deployed GW Veterans.

The definition was conceived when the Kansas Persian Gulf Veterans Health Initiative sponsored a study of deployment-related symptoms in 1998 (Steele, 2000). The investigators chose to develop a clinically based descriptive definition using correlated symptoms. Subjects were GW Veterans (2,030) living in Kansas who participated in a telephone interview. The researchers developed a case definition that required: (1) symptom onset after 1990; (2) presence of symptoms in the year before the interview; (3) no diagnoses or treatment for exclusionary conditions (cancer, diabetes, heart disease, chronic infectious disease, lupus, multiple sclerosis, stroke, or any serious psychiatric condition); (4) symptoms in at least three of six symptom groups (fatigue and sleep problems, pain, neurologic and mood, gastrointestinal, respiratory, and skin symptoms); and (5) at least one moderately severe symptom or two or more symptoms within a symptom group. The Kansas study found GWI to be more prevalent in those GW Veterans who were women, had lower income, had less education, served in the U.S. Army, and served as enlisted personnel.

The Haley Definition

A third system for defining GWI was developed by Haley, et al., (Haley, 1997). This case definition includes three distinct syndrome complexes that distinguish correlated clusters of GWI symptoms. Haley and colleagues employed factor analytic techniques from standardized questionnaires to evaluate symptom data from a Seabees unit, with 249 of the 606 members across five southeastern states participating. Because the original study lacked a comparison group, syndrome criteria were later validated against an independent cohort of Veterans in north Texas (Haley, 2001). The study initially defined six potential syndromes, but three primary syndromes emerged: Syndrome 1 (impaired cognition) is characterized by problems with attention, memory, and sleep along with depression; Syndrome 2 (confusion/ataxia) includes problems with thinking and cognitive processing, as well as balance and coordination; and Syndrome 3 (neuropathic pain), is defined primarily by joint and muscle pain. The clinical definition originally proposed by Haley, et al., captured 34% of the cohort, while the six initial factor-derived syndromes collectively identified 25% of the veterans.

Towards a Single GWI Case Definition

focused on the low and inconsistent rate of approvals of claims and the notification process for Veterans with GWI. It concluded that: “…the persistent lack of a single case definition for Gulf War Illness contributes to many of the current challenges with the Gulf War Illness disability compensation program.” This led to the following recommendation: “To increase the likelihood of making progress toward developing a single case definition of Gulf War Illness, we recommend that the Secretary of Veterans Affairs direct the Under Secretary for Health to prepare and document a plan to develop a single case definition of Gulf War Illness. This plan should include near- and long-term specific actions, such as analyzing and leveraging information in existing datasets and identifying any areas for future research to help VA achieve this goal.” In response, the VA’s Office of Research and Development and Office of Patient Care Services, Post-Deployment Health Services, convened a group of subject matter experts to develop a plan to address short- and long-term actions related to GWI. The group will review the current literature, analyze and leverage information in existing datasets, and identify areas for future research.

**Lack of Standard Treatments**

Clinical trials with the potential to have significant impacts on the health and lives of Veterans with GWI continue to be an ongoing priority. A primary focus of the GWIRP has been to fund research studies identify treatment targets and test interventional approaches to alleviate symptoms. While most of these studies remain in progress, several have already shown varying levels of promise as GWI treatments. Details of some of these studies have been published and can be found under the **Published Results** section below.

In the absence of treatments specific for GWI, Veterans have tried a myriad of over-the-counter and off-label drugs and therapies to treat their varied symptoms. Many have sought out complementary/alternative therapies and holistic medicines for relief. Physical modalities (yoga, sauna, physical therapy); lifestyle changes (diet change, exercise, avoidance of triggers); herbs, vitamins and nutritional supplements; alternative medicine practices (chiropractic modalities, acupuncture); and unconventional practices (continuous positive airway pressure [CPAP], hyperbaric oxygen therapy, chelation) have all been attempted by GW Veterans trying to ease their pain and other symptoms. A study of Mind-Body Bridging, a focused concentration method previously shown to be effective for improving disturbed sleep, found this technique to be more effective in reducing disturbed sleep in a cohort of symptomatic GW Veterans compared to a standard sleep education group. (Nakamura, 2017).

Ongoing trials of pharmaceutical interventions include repurposing U.S. Food and Drug Administration (FDA)-approved compounds targeting the major symptoms of GWI and are based on therapeutic targets identified in the model systems. The number of treatment studies
has dramatically increased in recent years; however, only a limited number of trials have published results to date.

GWI clinical trial investigators are regularly challenged to complete enrollment of both symptomatic and healthy GW Veterans and GW-era Veterans. The GWIRP has prepared a document to assist investigators in this process. The document, *General Guidance for Gulf War Veteran Outreach and Recruitment*, can be found on the GWIRP website ([http://cdmrp.army.mil/gwirp/pdfs/General%20_Guidance_for_Gulf_War_Veteran_Outreach_and_Recruitment.pdf](http://cdmrp.army.mil/gwirp/pdfs/General%20_Guidance_for_Gulf_War_Veteran_Outreach_and_Recruitment.pdf)).

**Published Results on Treatments**

The earliest federally funded multi-center clinical trials were VA- and DoD-funded trials that focused on antibiotic treatment (doxycycline) (Donta, 2004) and cognitive behavioral therapy with exercise (Donta, 2003). Neither intervention provided long-lasting improvement for a substantial number of Veterans.

Preliminary analysis from a placebo-controlled trial showed that 100 mg of Coenzyme Q10 (known as CoQ10 or Ubiquinone) significantly improved general self-reported health and physical functioning, including among 20 symptoms, each of which was present in at least half of the study participants, with the exception of sleep. These improvements included reducing commonly reported symptoms of fatigue, dysphoric mood, and pain (Golomb, 2014). These results are currently being expanded in a GWIRP-funded trial of a “mitochondrial cocktail” for GWI of CoQ10 plus a number of nutrients chosen to support cellular energy production and defend against oxidative stress. The treatment is also being investigated in a larger, VA-sponsored Phase III trial of Ubiquinol, the reduced form of CoQ10.

In a randomized, sham-controlled VA-funded trial of a nasal CPAP mask (Amin, 2011b), symptomatic GW Veterans with sleep-disordered breathing receiving the CPAP therapy showed significant improvements in fatigue scores, cognitive function, sleep quality, and measures of physical and mental health (Amin, 2011a).

Preliminary data from a GWIRP-funded acupuncture treatment study showed that Veterans reported significant reductions in pain and both primary and secondary health complaints, with results being more positive in the bi-weekly versus weekly treatment group (Conboy, 2012). Current studies funded by the GWIRP and the VA are also investigating yoga as a treatment for GWI.

An amino acid supplement containing L-carnosine was found to reduce irritable bowel syndrome-associated diarrhea in a randomized, controlled GWIRP-funded trial in GW Veterans (Baraniuk, 2013). Veterans receiving L-carnosine showed a significant improvement in performance in a cognitive task, but no improvement in fatigue, pain, hyperalgesia, or activity levels.

Results from a 26-week GWIRP-funded trial comparing standard care to nasal irrigation with either saline or a xylitol solution revealed that both irrigation protocols reduced GWI respiratory (chronic rhinosinusitis) and fatigue symptoms (Hayer, 2015).
Administration of the glucocorticoid receptor antagonist mifepristone to GW Veterans in a GWIRP-funded randomized trial resulted in an improvement in verbal learning, but no improvement in self-reported physical health or other self-reported measures of mental health (Golier, 2016).

Ongoing Intervention Studies
The GWIRP is currently funding many early-phase clinical trials aimed at GWI. Interventions include direct electrical nerve stimulation, repurposing FDA-approved pharmaceuticals, and dietary protocols and/or nutraceuticals. Both ongoing and closed GWIRP-supported clinical treatment trials and pilot studies can be found at http://cdmrp.army.mil/gwirp/resources/cinterventions.shtml.

Clinical Infrastructure and Collaborative Efforts
In fiscal year 2017, the GWIRP offered two large funding mechanisms to support multi-institutional collaboration and clinical infrastructure. A Biorepository Resource Network Award was offered to support development and maintenance of a GWI biorepository through a network of sites that will facilitate biospecimen and biological data collection, processing, annotation, storage, and distribution. A Clinical Consortium Award was offered to support a group of institutions, coordinated through an Operations Center that will conceive, design, develop, and conduct collaborative Phase I and II clinical evaluations of promising therapeutic agents for the management or treatment of GWI. These mechanisms were designed to build on the achievements of the previously established consortia and to further promote collaboration and resource sharing.

Through a collaboration among the NIH, CDC, VA, DoD GWIRP, and GWI community, CDE recommendations are being developed for GWI. The goals of this effort are to increase the efficiency and effectiveness of clinical research studies and treatment; increase data quality; facilitate data sharing and aggregation of information across studies; and help educate new clinical investigators. Development of CDEs is an iterative process, and updates are expected as research progresses and feedback is received from the community.

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