*WAR AND HEALTH (H. Tapamainen, ed., Zed Press, Helsinki, 1999, pp. 431-446)*

# GULF WAR ILLNESSES: ROLE OF CHEMICAL, RADIOLOGICAL AND BIOLOGICAL EXPOSURES

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## 1. INTRODUCTION: MULTIFACTORIAL ILLNESSES OF THE GULF WAR

Gulf War Syndrome and Gulf War Illnesses (GWI) are terms that have been used to describe a collection of chronic signs and symptoms reported by U.S., British, Canadian, Czech, Danish, Saudi, Egyptian, Syrian, Moroccan and other Coalition Armed Forces that were deployed to Operation Desert Storm (ODS) in 1991. Over 100,000 American veterans of Desert Storm/Shield (approximately 15% of deployed U. S. Armed Forces) returned from the Persian Gulf and slowly (6-24 months or more) presented with a variety of complex signs and symptoms characterized by disabling fatigue, intermittent fevers, night sweats, arthralgia, myalgia, impairments in short-term memory, headaches, skin rashes, intermittent diarrhea, abdominal bloating, chronic bronchitis, photophobia, confusion, transient visual scotomata, irritability and depression and other signs and symptoms that until recently have defied appropriate diagnoses (1-3). These symptoms are not localized to any one organ, and the signs and symptoms and routine laboratory test results are not consistent with a single, specific disease (1).

The signs and symptoms of GWI have been reported by 27/28 of the Coalition Armed Forces that were deployed against Iraqi units in Kuwait and Southern Iraq. The only exception is France. This brief review will summarize some of the possible exposures that occurred, the types of illnesses that resulted from these exposures, and some of the treatments that have been used on GWI patients. Because of space limitations, these topics cannot be discussed in detail. Instead, they are summarized along with a few references that should be useful.

### 1.1 The Signs and Symptoms of GWI

Most investigators who study Gulf War Syndrome or GWI do not believe that it is a separate, new syndrome (2, 3). However, there are unique characteristics of the illnesses. GWI has been called Mucocutaneous-Intestinal-Rheumatic Desert Syndrome by Murray-Leisure et al. (4), who reported illnesses in Desert Storm veterans that did not fit standard U. S. Veterans' Administration diagnosis categories. Murray-Leisure et al. (4) placed patients into three broad categories: (a) Mucocutaneous lesions with pustular dermatitis, (b) Intestinal disorders with irritable bowels and (c) Rheumatic complaints of large-joint polyarthralgias with night sweats. Minor criteria included: heartburn, rectal fissures, bleeding or hemorrhoids, lactose or meat intolerance, splenomegaly and splenic tenderness, weakness and/or chronic fatigue, headaches, muscle aches, polymyalgias, memory loss, hair loss, fevers of unknown origin, unexplained leukocytosis or neutropenia, nasal ulcers or sores, chronic sinus or nasal congestion, atypical chest pain, new-onset asthma or chronic bronchitis, ear infections or tinnitus and dental infections. In addition, Haley et al. (3) found several different neurological diagnoses in GWI patients, indicating that simple disease categories for GWI patients may prove to be elusive. Veterans of a U. S. Navy Mobile Construction Reserve Battalion were analyzed, and Haley et al. (3) found evidence of neurologic injury involving the central, peripheral and autonomic nervous systems in patients with GWI. Baumzweiger and Grove (5) have described GWI as neuro-immune disorders that involve the central, peripheral and autonomous nervous and immune systems. They attribute a major source of illness to be brainstem damage due to central, peripheral and cranial nerve neuropathy with demyelination. Patients tend to have muscle spasms, memory deficits, attention deficits, Ataxia, and increased muscle tone, which are often seen in neurotoxin-induced brain stem dysfunction (5). GWI patients can also have chronic bacterial and viral infections that are an important source of morbidity (2, 6, 7).

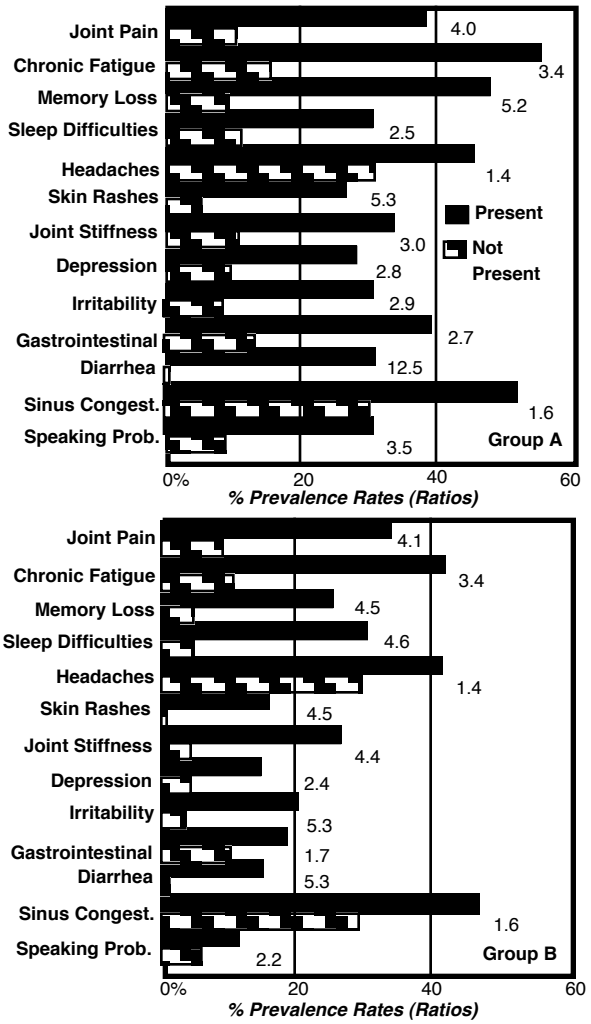
Although the chronic signs and symptoms of GWI usually do not result in illnesses that progress to cause death (8), there are now thousands of U. S. Desert Storm veterans dead from a variety of illnesses that may have been obtained from their service (6). The possible reasons why these deaths have not been reported in official studies of the problem could be due to the limited sizes of study groups and time intervals used for analysis, the lack of information on veterans who have left the Armed Forces, and the primary use of military hospitals for the analysis (4). In the U. S. estimates of between 8,000 and 15,000 or more dead have been advanced, but the exact figures may never be known. Although for years the U. S Department of Defense and U. K. Ministry of Defense officially stated that there were no illnesses associated with deployment to Desert Shield/Storm, just the opposite has been found (9), bringing into question whether "official" U. S. or British government studies will ever acknowledge the problem (10, 11).

That veterans with GWI have chronic illnesses at higher rates than military personnel from the same units that were not deployed to the Persian Gulf was shown in a case control study performed by the U. S. Center for Disease Control (9). In the reserve and national guard units studied hundreds of soldiers or airmen that were deployed to the Persian Gulf region were compared to similar numbers of soldiers or airmen from the same units that were not deployed (Figure 1, two units are shown). In the four units that were studied, the deployed soldiers had a variety of chronic illness signs and symptoms that were not present in the same frequencies in the nondeployed men and women (9). For certain signs and symptoms, this difference was dramatic (for example, over 13-times higher incidence of diarrhea in deployed personnel). This study showed that deployment to the Kuwaiti Theater of Operations (KTO) was an underlying risk for obtaining chronic illnesses.

### 1.2. Post Traumatic Stress Disorder: an Unlikely Diagnosis for GWI

Although it has been generally accepted that many Gulf War veterans have medical problems, as mentioned above, the signs and symptoms of GWI are not well established as criteria for particular illnesses, and they do not readily fit into the common ICD-9 diagnosis categories used by military and veterans' hospitals (1-3). This has resulted in many veterans receiving diagnoses described as an "unknown" disorder, or GWI patients have been diagnosed with psychological problems, such as Post Traumatic Stress Disorder (PTSD) (1, 10, 11). Most physicians and scientists that work on GWI do not accept that GWI can be easily explained by psychiatric or psychological diagnoses, nor can

**Figure 1.** Control study on Gulf War illnesses conducted by the CDC. The bars indicate the frequencies of common symptoms in deployed (solid bars) and non-deployed (stippled bars) members of Air National Guard (Unit A) and Air Force Reserve (Unit B) units where approximately equal numbers of airmen were deployed or not deployed to the Arabian Gulf region. The numbers by the solid bars indicate the ratio of prevalence (data from reference 9).




they be successfully treated as somatization disorders (4-6). Unlike PTSD, GWI has a number of significant signs that are different, such as neuro-muscular problems, skin disorders, gastrointestinal problems, muscle and joint pain and temperature abnormalities (intermittent fevers). That many of the reported signs and symptoms do not fit the diagnosis of PTSD has not stopped military and veterans' hospitals from liberally using this diagnosis for GWI and treating GWI patients accordingly (1, 3).

### 1.3 Similarity of GWI to Chronic Fatigue Syndrome and Fibromyalgia Syndrome

The variable incubation time of GWI, ranging from months to years after presumed exposure, the cyclic nature of the relapsing fevers and the other chronic signs and symptoms and their appearance in immediate family members are consistent with an organic disease (2, 3, 5, 6). The syndromes most similar to GWI are Chronic Fatigue Syndrome (CFS) (often termed myalgic encephalomyelitis) and Fibromyalgia Syndrome (FMS) (2, 7). We have proposed that the signs and symptoms found in many GWI patients may be caused by chronic exposures to chemical mixtures and host responses to infectious agents, resulting in cytokine production and a variety of other responses that result in a CFS- or FMS-like disorder (2). When the signs and symptoms of GWI were compared to the signs and symptoms of CFS, the similarity was striking (Figure 2) (2). CFS is primarily characterized by persistent or relapsing, debilitating fatigue or easy fatigability in a person who has no previous history of similar symptoms, that does not resolve with rest and is severe enough to reduce or impair average daily activity below 50% of the patient's premorbid activity level. In addition to the absence of clinical conditions that could easily explain the symptoms, such as malignancies or autoimmune diseases, patients present with mild fever, sore throat, arthralgia, myalgia, generalized muscle weakness, headaches, painful lymph nodes, sleep difficulties, and neuropsychologic complaints, such as memory loss, photophobia, confusion, transient visual scotomata, irritability and depression. These signs and symptoms closely parallel those found in GWI (Figure 2) (2). This indicates that GWI is not a separate or "new" syndrome; it is a CFS-like disorder (2). The signs and symptoms of GWI also overlap with FMS, a condition similar to CSF but one that has polymyalgia as its major sign/symptom and does not necessarily involve cognitive problems.

There are some differences between GWI and CFS/FMS that may be important in determining the various possible causes of GWI. Baumzweiger and Grove (5) have stressed that unlike CFS and FMS, GWI is associated with Ataxia and increased motor tone, symptomatic of brainstem dysfunction. They have described three different forms of GWI. "Simple" GWI is described as brainstem problems secondary to other disorders, such as infections; "Complex" GWI is similar to "Simple" GWI but with brainstem, autonomic, cranial nerve and peripheral nerve demyelination occurring as well. In the third "Neurotoxic" GWI form two or more specific neurotoxic, viral/microbial or physical traumatic "hits" to the brain stem occur, resulting in severe brainstem inflammation, limbic system involvement and personality behavioral changes. These categories of GWI may prove useful in determining the role of various exposures in the progression of GWI.

## 2. POSSIBLE CAUSES OF GWI

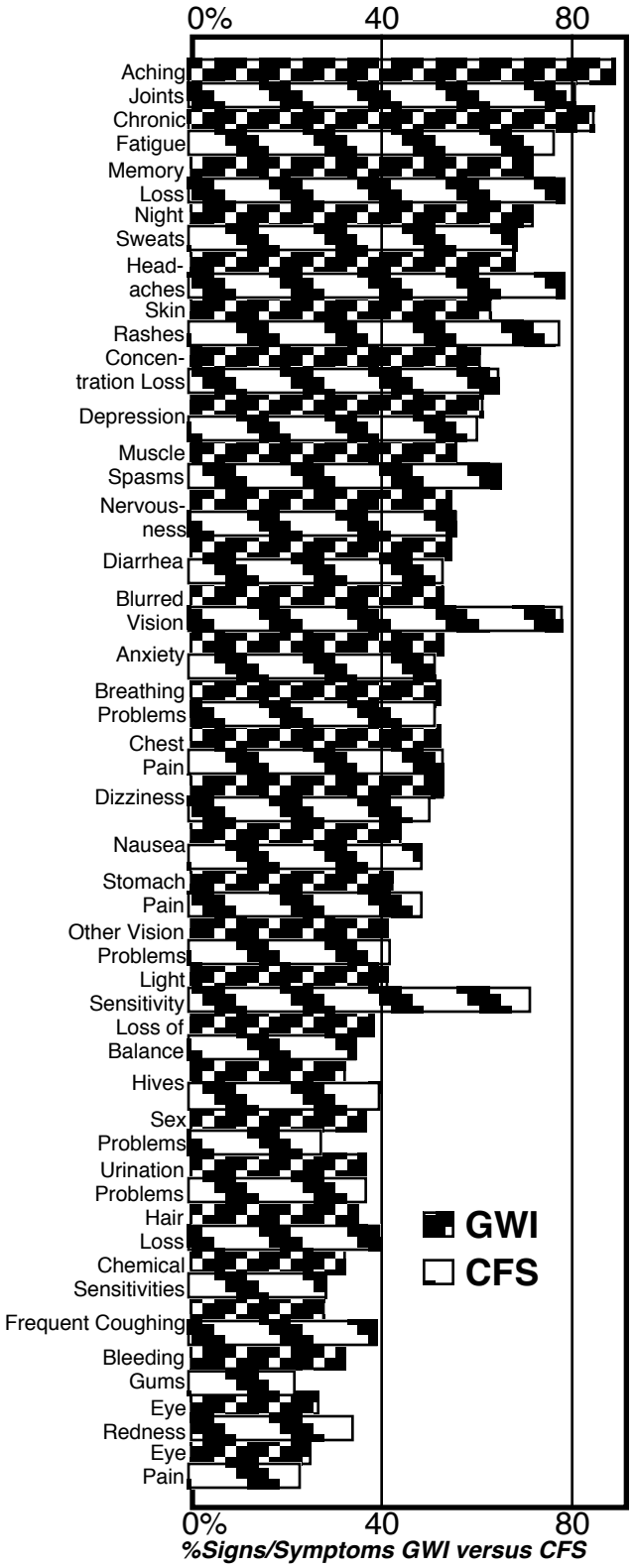
Part of the confusion in diagnosing GWI is that the overlapping chronic signs and symptoms displayed by GWI patients can be caused by quite different types of exposures. Veterans of the Gulf War could have been exposed to chemical, radiological and/or biological agents, or more likely combinations of these exposures (Figure 3) (5-7, 11). Accurate diagnosis and successful treatment of GWI will depend on identifying the underlying exposures involved, because the illnesses caused by toxic exposures are treated differently if their origins are chemical, radiological or biological.

### 2.1 Chemical Exposures

Veterans of the Gulf War were exposed to a variety of chemicals, including insecticides such as the insect repellent N,N-dimethyl-m-toluamide and the insecticide permethrin, battlefield smoke and fumes and smoke from burning oil wells, use of the anti-nerve agent pyridostigmine bromide, solvents used to clean equipment and a variety of other chemicals, including in some cases, possible exposures to low levels of Chemical Warfare (CW) agents (10, 11). Although contentious , this last source of chemical exposure (CW agents) may have occurred due to destruction of CW stores in factories and storage bunkers during and after the war as well as possible offensive deployment of CW agents (10, 11).

Low level exposures to mixtures of chemicals, particularly organophosphates and other chemicals, can result in chronic illnesses, including chronic neurotoxicity and immune supression, and these probably play an important role in many GWI cases (Figure 3) (3, 11, 12). Abou-Donia and Wilmarth (12) found that combinations of

**Figure 2.** Prevalence of common signs and symptoms found in 650 patients with GWI compared to literature values for CFS (data from reference 2).




pyridostigmine bromide, N,N-dimethyl-m-toluamide and permethrin produce neurotoxicity, diarrhea, salivation, shortness of breath, locomotor dysfunctions, tremors, and other impairments in healthy adult hens. Multiple Chemical Sensitivity Syndrome (MCS) and Organophosphate-Induced Delayed Neurotoxicity (OPIDN) are examples of chronic illnesses caused by multiple chemical exposures (13). Patients with these syndromes can present with many of the signs and symptoms found in GWI patients, and in fact, many GWI cases may eventually be explained by complex chemical exposures in the Gulf. In these patients, memory loss, headaches, cognitive problems, severe depression, loss of concentration, vision and balance problems, chemical sensitivities, among others, typify the types of signs and symptoms found in chronic chemically exposed patients (13).

For the most part, the GWI signs and symptoms began to present between 6 months to two years or more after the end of Operation Desert Storm. The slow onset of clinical signs and symptoms in chemically exposed individuals is typical for Organophospate-Induced Delayed Neurotoxicity. Of particular concern was the possibility that low levels of CW agents were present in the Persian Gulf region from the bombing of CW factories in Iraq and storage facilities (and their demolition after the war by Engineering units) in Iraq and Kuwait, and the offensive use of CW delivered by SCUD B (SS1) or FROG missiles, aircraft or vehicles outfitted with CW sprayers or by artillery shells and rockets, CW mines and other sources (10, 11).

Iraqi Armed Forces were known to have extensive stores of such weapons, and intelligence reports indicated that orders to use offensive CW agents against Coalition Forces were given down to the Battalion level during the conflict. In testimony to the U. S. Congress, Army CBW officers indicated that over 14,000 CW alarms sounded during but not before or after the Gulf War air/ground offensive, and some soldiers were given medals for identifying the types of CW that were released in the KTO (10). Extensive stockpiles of mustard (blister agent HN or HT), lewisite (blister agent L), sarin (nerve agent GB or GF), tabun (nerve agent GA) and other CW agents were present in the KTO, and extensive stores of these weapons were released into the atmosphere during the air campaign and by the destruction of Iraqi storage bunkers after the conflict (10, 11). Low level exposure to nerve agents combined with other organophosphate exposures may have resulted in large numbers of delayed casualties and GWI.

### 2.2 Environmental Hazards and Nontransmittible Biological Exposures

Several possible environmental hazards were present in the KTO. In addition to the chemicals released by burning oil well fires and ruptured petroleum pipelines, soldiers were exposed to fine, blowing sand. The small size of the sand particles (much less than 1 mm) and the relatively constant winds in the region resulted in some inhalation of small silica particles. The presence of small sand particles deep in the lungs can produce a pulmonary inflammation or disorder that can progress to pneumonitis. This form of pneumonitis has been called Al-Eskan Disease (14), and it usually presents as a pneumonia or flu-like condition that can eventually progress to more widespread signs and symptoms, including fibrosis, immunosuppression and opportunistic infections. Although it is extremely doubtful that most GWI is Al-Eskan Disease, the presence of silica-induced immune suppression in some soldiers could have resulted in the appearance of chronic infections in these patients (14).

Parasites such as Leishmaniasis and Schistosomiasis and bacteria that cause Malaria and Cholera are endemic to the Middle East and could be the cause of illnesses in at least some of the veterans with GWI (4). Characteristic signs and symptoms occur in these illnesses, and diagnostic tests are available for most of these agents. Moreover, there have been no reports that they are the cause of illness in large numbers of patients with GWI. In some patients infections by *Leishmania tropica*, spread by the sandfly *Phlebotomus papatasi* may be involved. This type of infection can result in viscerotropic Leishmaniasis and elevated temperature,

lymphadenopathy and hepatosplenomegaly (15). However, most of the common signs and symptoms of GWI do not fit with this explanation, and diagnosis of Leishmaniasis is relatively uncommon (estimated at less than one hundred) in Gulf War veterans. Nonetheless, it is unclear how prevalent Leishmaniasis infections are in GWI patients.

Biological toxins were also present in the KTO (10). The Iraqi Army had ample stores of aflatoxin (*Aspergillus flavus* toxin), ricin (from *Ricinus communis* beans), *Clostridium botulinum* toxin and possibly other toxins. Another type of toxin that is potentially dangerous is the tricothecene mycotoxins produced by various species of fungi. Mycotoxins act quickly by direct cutanous contact and cause erythema accompanied by blisters, wheezing, pain and burning sensations. Some of these toxins can be fatal in very low doses (inhaled ricin in extremely small doses can cause inflammation of the respiratory mucosa with hemorrhage into the lungs or edema, hemorrhage of the GI tract and death within 8-72 hours) or cause delayed carcinogenic or immunosuppressive effects (aflatoxin exposure). The preferred method of delivery of these toxins was by BW sprayer onto the sand or by aircraft (11). Over 50 Italian-made BW sprayers were found fully deployed in Southern Iraq and Western Kuwait, and aircraft fitted with BW sprayers were captured by U. S Forces at airfields in Southern Iraq.

Murray-Leisure et al. (4) have described another aspect of GWI, its association (noninhalation) with sand exposure. This is most likely caused by a chronic transmittable infection found in sand that is endemic to the region. The risk for sand-associated illness appeared to be highest in the months of August, September or October. Although no infections were identified, the slow appearance of the same signs and symptoms in spouses and children of veterans with GWI suggested that a slow-growing microorganism was being transferred by mucocutaneous, sexual or transplacemental mechanisms but probably not by causal contact (see 2.4, below). Anthrax, caused by the Gram-positive *Bacillus anthracis*, a commonly used BW agent, is often found in soil. It can gain entrance through skin wounds but also by inhalation or ingestion. Anthrax infection does not result in a chronic illness, however, because its signs and symptoms, such as malaise, fever, fatigue, headache, respiratory distress and other more severe signs and symptoms, usually appear in 1-6 days of exposure.

### 2.3 Radiological Exposures

An important contaminant of the battlefield environment in the Gulf War was depleted uranium (DU) (6). DU, a by-product of uranium processing for civilian and military use, was used in armor-penetrating ammunition and in protective armor on tanks and other vehicles because of its hardness and high density. Depleted uranium contains about 30% of the normal amount of U-235, a dangerous radioisotope with a half-life of over 4 billion years (6). When a DU penetrator hits an armored target, it disintegrates due to the resulting kinetic energy transfer that results in high temperatures. DU rapidly oxidizes at high temperature, resulting in the formation of uranium oxide particles. The uranium oxide particles that form from disintegration of DU penetrators are usually small, and due to their high density they probably settled on damaged armored vehicles, reinforced bunkers and onto the surrounding sand. Uranium oxide particles can be easily inhaled along with smoke or fine sand. If even one small particle of less than 5 micrometers in diameter is trapped in the pulmonary system, the lungs and surrounding tissues can be exposed over a year to up to 272-times the annual whole body radiation dosage permitted radiation workers by U. S. regulations (6). Fortunately, exposure can be monitored, and studies on the radiation exposures of Gulf War veterans should be initiated as soon as possible to determine the prevalence and extent of uranium oxide exposure.

In addition to battlefield contamination with DU, civilian nuclear reactors in Iraq were destroyed during the air campaign. This may have resulted in the release of long half-life isotopes like Sr-90, U-235, Co-90 and other dangerous isotopes into the air. Similar to the bombing of CW and BW factories and storage facilities, this could have resulted in some blow-back into Coalition Forces, since the prevailing winds in the region were generally from the Northwest to Southeast. Unfortunately, there appears to be no available assessment of the contamination to the region from the release of nuclear reactor materials into the environment.

### 2.4. Transmittable Biological Exposures

There is some evidence for the presence of transmittable biological agents in GWI patients. In many cases, the veterans' immediate family members appear to have the same or similar signs and symptoms (4, 7, 16, 17). One estimate derived from inquiries from over 1,200 GWI families indicated that approximately 77% of spouses and 65% of children born after the Gulf War now have the signs and symptoms of GWI (18). When immediate family members presented with the same or similar illness, the onset of their GWI signs and symptoms usually occurred from 6 months to one year or more after the onset of the veteran's illness, and not every family member developed GWI signs and symptoms. Because of the apparent slow rate of transmission of GWI to immediate family members, the general public is probably not at high risk for contracting GWI from casual contact with GWI patients (4, 7). Veterans with transmittable biological exposures could have received these through natural means (soil, water, etc.), or they could have obtained their exposures from contaminated vaccines, Iraqi BW sprayers, BW warheads on SCUD or FROG missiles or artillery , or from "blow-back" contamination after the destruction of BW factories and storage bunkers (11).

In support of a biological hypothesis for a subset of patients with GWI, infectious agents have been found in GWI patients' urine (6) and blood (16, 17). Using a microscopic technique for determining bacterial infections in urine, Hyman (19) has found that many Gulf War veterans show evidence of bacterial infections that can be successfully treated with several courses of broad spectrum antibiotics. We found that most of the GWI symptoms can be explained by chronic pathogenic bacterial infections, such as mycoplasmal infections (16, 17, 20). Mycoplasmal infections usually produce relatively benign diseases limited to particular tissue sites or organs, such as urinary tract or respiratory infections (20). However, the types of mycoplasmas that we have detected in Desert Storm veterans, such as *Mycoplasma fermentans* (incognitus) that may be causing many of the chronic fatigue and other signs and symptoms of GWI, are very pathogenic, colonize a variety of organs and tissues, and are difficult to treat (16, 17). In studies of over 200 patients, including both U. S. and British veterans with GWI and their symptomatic family members, evidence of mycoplasmal infections has been found in about one-half (45%) of the GWI patients' blood leukocyte samples (16, 17). The incidence of mycoplasmal infections in nondeployed, healthy subjects was found to be approximately 5% (17). The appearance of mycoplasmas in the leukocytes of some controls could indicate that these individuals are in a very early stage of the illness or that they are nonsymptomatic carriers of the infection.

Since the group of mycoplasma-positive patients may be more symptomatic than the average GWI patient, it is likely that the final incidence of mycoplasmal infections in GWI will be lower than the incidence rate reported above (16, 17). In addition, not every Gulf War veteran had the same type of mycoplasma DNA sequences inside their white blood cells, although the most common infection found by far was *Mycoplasma fermentans* in GWI patients. Interestingly, when civilian patients with CSF or FMS were examined for systemic mycoplasmal infections, high frequencies of

mycoplasmal infections were also found (approximately 60%), indicating another link between these disorders. The main difference was that in addition to *Mycoplasma fermentans* several other species of mycoplasmas were found in civilians with CSF or FMS (21).

Preliminary evidence suggests that the *Mycoplasma fermentans* found inside white blood cells of GWI patients may have been modified to make it more pathogenic and more difficult to diagnose. Using the Nucleoprotein Gene Tracking assay we have found unusual gene sequences associated with the same mycoplasma nucleoprotein fraction. For example, we have found HIV-1 *envelope* gene sequences but not the other genes of the HIV-1 virus in equivalent nucleoprotein subfractions in a subset of GWI patients (17). Although this preliminary result will require conformation by sequencing the mycoplasma genome in the area of the putative inserted gene, the presence of the HIV-1 *env* gene could explain the unusual pathogenic properties of this mycoplasma and its ability to attach to and enter a variety of cells and tissues. Since the other genes of the HIV-1 virus were not detected in ODS veterans, these mycoplasma-positive GWI patients are not infected with the intact HIV-1 virus. Although GWI patients possess some of the signs and symptoms of an immunodefficiency syndrome, they do not progress to AIDS, nor do they test generally positive for intact HIV-1 virus in their serum or plasma (unpublished data). Some GWI patients, however, do test positive (false positive) in some AIDS tests that probe only the gp120 product of the HIV-1 *env* gene. In these patients additional testing for other HIV-1 gene products or enzymes has proved negative, suggesting support for the hypothesis that only the HIV-1 *env* gene and its encoded product are associated with *M. fermentans* infection of the type found in some GWI patients.

Other chronic infections have also been found in GWI patients. For example, some evidence for *Brucella* infections has been found in some GWI cases by us using Forensic Polymerase Chain Reaction (Unpublished observations). This is in contrast to official reports by the Walter Reed Army Institute of Research (22). Inhalation of *Brucella spp*. (*Brucella melitensis* strains predominantly) can cause the slow onset of brucellosis, a chronic illness that shares many but not all of the signs and symptoms of GWI. The prevalence of *Brucella spp.* infections has not been carefully determined in GWI patients.

Other possible infections (not limited to chronic agents) include Q Fever, caused by *Coxiella burnetii,* anthrax caused by *Bacillus anthracis,* botulism caused by the botulinum toxin released from *Clostridium botulinum,* and other possible BW agents. A report has appeared on Q fever meningoencephalitis in a GWI patient (23). Other possible transmittible diseases are those carried by zoonotic sources, such as Plague forming *Yersinia pestis*, a gram-negative, non-spore forming bacillus obtained from the bite of insects (fleas), or Malaria, caused by *P. falciparum* or *P. vivax* from the bite of infected Anopheline mosquitos. Airborne virus-caused diseases, such as Viral Hepatitis caused by Hepatitis viruses, might be a secondary problem in some GWI cases. Most of the signs and symptoms of these infections are more acute, however, than those found in GWI patients.

## 3. TREATMENT OF GWI

### 3.1 Chemical Exposures

The treatment of chemically exposed patients usually involves removal of offending chemicals from the patient's environment, depletion of chemicals from the patient's system and treatment of the signs and symptoms caused by chemical exposure(s) (13, 24). Chemically exposed patients are often extremely sensitive to a variety of commonly encountered chemicals, including perfumes and air freshners, petrochemical fumes, chlorine, cleaning solutions and solvents, among others. They are also very sensitive to certain foods, and special diets are often necessary, and in some cases direct skin contact with certain substances can cause strong cutaneous reactions. Therefore, an important part of treatment for chemical exposures requires limiting exposures to a variety of common chemicals and gradual removal of toxic chemicals (13, 24).

Patients with MCS or OPIDN benefit from procedures that slowly remove chemicals from their bodies. We recommend dry saunas for help in chemical removal, as well as magnesium sulfate-hydrogen peroxide baths (see 3.5). Unfortunately, some GWI patients may have irreversible nerve damage due to low level nerve agent exposure potentiated by the effects of the antinerve agent pyridostigmine bromide. Nonetheless, most chemical contamination can be reduced through a program of heat depuration, physical therapy and nutritional supplementation in a specially constructed less chemically contaminated environment as described by Rea et al. (24). In this program, patients receive up to 2 hours/day of heat (average 75 min/day, essentially dry saunas at 140-160°C) in divided doses with graded exercise (average 60 min/day) and massage (average 45 min/day). They also receive purified water, vitamins (initially iv vitamin C 15 g/day for 5-7 days, then 2-8 g/day oral vitamin C, 10,000-25,000 IU/day vitamin A, and 400-800 IU/day vitamin E plus others), minerals (1000 mg/day calcium, 500 mg/day magnesium, 30-60 mg/day zinc, 200 mcg/day selenium, 10 mg/day manganese, 500-1000 mg/day chromium and 2 mg/day copper plus others) and antioxidants (3 X 75 mg per day reduced glutathione) and 600 mg/day ketoglutaric acid. Using this program over 63% of over 200 patients studied reduced their levels of toxic chemicals and showed improvements in chemical sensitivity (24).

In addition to heat, exercise and diet, a variety of medications can alleviate some of the signs and symptoms of chemical exposures in GWI patients. Many patients have benefited from anti-anxiety, anti-depressant and anti-inflammatory drugs (5), but this may not be beneficial for some GWI patients. Baumzweiger and Grove (5) have recommended use of dihydropyridine calcium channel blockers in GWI patients to normalize the neurotoxic effects of chemical exposures. After placing 111 GWI patients on dihydropyridine calcium channel blockers, they noted that neurological signs and symptoms improved. For example, heart rate acceleration, blood vessel irritability, neuro-psychiatric and neuro-immune status improved in patients on the calcium channel blockers Nimodipine, Amlodipine or Felodipine. During medication with calcium channel blockers Forinef is sometimes needed for blood pressure support. Baumzweiger and Grove (5) also recommend the psychoactive medications Bupropion (Wellbutrin) and Amantadine (Symmetrel) for cognitive deficits and the extra pyramidal signs and symptoms and Trazodone benzodiazepines for insomnia.

### 3.2 Radiological Exposures

The successful treatment of patients exposed to DU depends on the extent of exposure. Most patients would have been exposed to DU by inhalation of uranium oxide particles. Such particles can remain inert in the lungs for extended periods of time, resulting primarily in local tissue alpha irradiation and the resulting radiation damage and immune suppression. Systemic U-235 can be removed by chelation therapy, usually with ethylenediaminetetraacetic acid (EDTA) or penicillamine. Using chelation therapy heavy metals can be removed from the circulation and tissues, and this procedure also aids in the breakdown of the plaques that line the arteries and cause arteriosclerosis. Successful chelation therapy requires slow iv infusion of the chelation agent (usually EDTA) in a course of 20-30 separate treatments. Although EDTA can be taken orally, only about 5% or less is actually absorbed. Nutrients such vitamin C, the amino acids L-cysteine and L-aspartic acid have been used to remove heavy metals but they only weakly chelate

heavy metal ions, although they also protect against free radical and ionizing radiation damage.

### 3.3 Biological Exposures

If infectious microorganisms are identified in GWI patients, they can be treated with the appropriate antibiotics. Treatment with antibiotics should result in improvement and even recovery in patients exposed to bacteria or mycoplasmas, such as *Mycoplasma fermentans* (20, 21). This is what has been found with many GWI patients (16, 17). The recommended treatments for systemic mycoplasmal infections require long-term antibiotic therapy, usually multiple 6-week cycles of doxycycline (200-300 mg/day), ciprofloxacin (Cipro; 1,500 mg/day), azithromycin (Zithromax; 500 mg/day) or clarithromycin (Biaxin; 500-750 mg/day) (25). Multiple cycles are required, because few patients recover after only a few cycles (17), possibly because of the intracellular locations of mycoplasmas, the slow-growing nature of these microorganisms and their inherent resistance to antibiotics. For example, 87 GWI patients that tested positive for mycoplasmal infections were treated with antibiotics. All patients relapsed after the first 6-week cycle of therapy, but after up to 6 cycles of therapy 69/87 patients recovered and returned to active duty (16, 17). Once patients recovered and were able to return to active duty or normal activity, mycoplasma gene sequences could no longer be detected in their blood leukocytes. The clinical responses that are seen are not due to placebo effects, because administration of some antibiotics that are not effective against mycoplasmal infections, such as penicillins, resulted in patients becoming more not less symptomatic, and they are not due to immunosuppressive effects that can occur with some of the recommended antibiotics. Interestingly, CFS, FMS and GWI patients that slowly recover after several cycles of antibiotics are generally less environmentally sensitive, suggesting that their immune systems may be returning to pre-illness states. If such patients had illnesses that were caused by psychological or psychiatric problems or solely by chemical exposures, they should not respond to the recommended antibiotics and slowly recover. In addition, if such treatments were just reducing autoimmune responses, then patients should relapse after the treatments are discontinued.

### 3.4 General Nutritional Suggestions

Patients with CFS, FMS or GWI usually have nutritional and vitamin deficiencies that must be corrected (25). For example, these patients are often depleted in vitamins A, B, C and E and certain minerals (see 3.1). Unfortunately, patients with these chronic illnesses often have poor absorption. Therefore, high doses of some vitamins must be used, and others, such as vitamin B complex, cannot be easily absorbed by the gut, so sublingual *natural* B-complex vitamins in small capsules or liquids is prefered. General vitamins plus extra C, E, CoQ-10, beta-carotene, folic acid, bioflavoids and biotin are essential (25). L- cysteine, L-tyrosine, L-carnitine and malic acid can also be useful. Certain minerals are also often depleted in GWI/CFS/FMS patients, such as zinc, magnesium, chromium and selenium (24) (see 3.1). Use of antibiotics that deplete normal gut bacteria can result in over-growth of less desirable flora, so *Lactobacillus acidophillus* supplementation is recommended (25).

A number of natural remedies that boost the immune system, such as herbal teas, whole lemon/olive extract drink, an extract of olive leaves with antioxidants, milk whey proteins, among others, are available and are potentially useful in GWI patients. Although these products appear to help some patients, their clinical effectiveness in GWI, CFS or FMS patients has not been carefully evaluated. They appear to be useful during therapy to boost the immune system or after therapy in a maintenance program to prevent relapse of illness (25).

### 3.5 Other Considerations

In general, GWI patients should practice avoidance of offending or irritating environments. They should avoid direct sunlight and chemical exposures whenever possible. Also, GWI patients are often taking multiple drugs that specify sunlight avoidance. Many GWI patients have been placed on anti-depressants and anti-anxiety medications without consideration of the source of their illness or other considerations, such as chemical and biological exposures. Although such mediations can alleviate temporarily some of the signs and symptoms of GWI, they are unlikely to recover from their chronic illness on these drugs alone.

For chemically and biologically exposed GWI patients, oxidative therapy has proved to be useful for some patients. We recommend magnesium sulfate-hydrogen peroxide baths for oxygenation of skin and underlying tissues. Hydrogen peroxide (3% solution) can also be directly applied to the skin and used for oral irrigation (1% solution) (25). Oxygenation therapy (iv hydrogen peroxide or ozone) appears to be much more commonly used in Europe than in North America.

## 4. CASE DESCRIPTIONS

### 4.1 Subject A.

Subject A was a U.S. Air Force Intelligence officer attached to the 5th Special Forces Group based at King Fahd Airport west of Dhahran and the 160th Special Operations Unit at King Khalid Military City. After his return to the U.S., he noticed that he had a constant sore throat, night sweats, fever, shortness of breath, dizziness, joint pain, short term memory loss, vision problems, diarrhea and other bowel problems, skin rashes and severe to moderate fatigue. He eventually left the Air Force and could not obtain treatment from Veterans hospitals for his GWI/FM/CFS. He tested positive for *M. fermentans,* received four 6-week courses of doxycycline and has completely recovered. Upon his recovery, he was retested for *M. fermentans* infection, and he had reverted to a mycoplasma-negative blood test.

### 4.2 Subjects B, C and D.

Subject B was a U.S. Army officer who served with the 101st Airborne Division (Air Assault). He was deployed on the deep insertions into Iraq. His unit did not come under enemy fire, and he considered his service relatively uneventful, until months after he returned to the U.S. What started out as a relative benign series of flu-like illnesses became progressively worse with intermittent fever, coughing, nausea, gastrointestinal problems, skin rashes, joint pain, memory loss, vision problems and severe headaches. Within 6 months after he presented with GWI/FM/CFS, his wife began to have chronic fatigue and gynecological problems, aching joints, headaches, and her stomach began to swell, causing severe pain. Their 7 year-old daughter then became ill with similar flu-like symptoms that did not go away and progressively became worse, resulting in chronic fatigue, skin lesions, vomiting, headaches, aching joints, and inability to gain weight. She was diagnosed with 'failure to thrive.' Several other families of Gulf War veterans at his base had similar health problems. These families were being told that their symptoms were the result of psychological problems (PTSD), but their symptoms were more consistent with GWI/FM/CFS. Subject A and his entire family tested positive for *M. fermentans* infection and were placed on several 6 week cycles of doxycycline. The entire family has almost completely recovered, but the veteran still shows some signs of chemical exposure/damage.

### 4.3 Subject E.

Subject E was a U.S.Army Special Forces officer assigned to a Military Intelligence Unit in the 101st Airborne Division (Air Assault). He was involved in reconnaissance missions and entered areas in Southern Iraq where animals and humans were dead from unknown causes. He slowly

presented with severe chemical sensitivities, chronic fatigue, intermittent fevers, coughing, nausea, gastrointestinal problems, skin rashes, joint pain, memory loss, vision problems and severe headaches. He was diagnosed with MCS and mycoplasmal infection. Due to his chemical sensitivities he was unable to continue the course of antibiotics necessary to treat the mycoplasmal infection, and he has not received all of the necessary treatments for his MCS. Through chemical avoidance, heat depuration and physical therapy, he has made a partial recovery, but he still has some of the signs and symptoms of GWI.

### 4.4 Subject F.

Subject F is a U.S. Air Force nurse who served in the medical evacuations units that operated at several locations in the Persian Gulf, but was not near combat areas. She presented with chronic fatigue, intermittent fever, stomach cramps, joint pain, skin rashes, memory loss, headaches, severe minstrel problems, uterine swelling and other symptoms. She tested positive for mycoplasmal infection and was placed on ciprofloxacin and then doxycycline for several 6 week cycles. She has completely recovered.

### 4.5 Subject G.

Subject G was a U.S. Army noncommissioned officer assigned in a support unit in Saudi. He presented with chronic fatigue, joint pain, skin rashes, memory loss, severe headaches and heart pain and other signs and symptoms. He was admitted to the Coronary Care Unit of a Major Medical Center with a massive heart attack. Echocardiograms indicted significant loss of heart function, and he was scheduled for a heart transplant. While awaiting a donor in the CCU, he was tested for mycoplasmal infection. He tested positive and was placed on iv doxycycline therapy, followed by oral doxycycline for several months. He responded to the antibiotics, and his echocardiograms showed significant improvement in heart function (from less than 15% function to over 50%). He eventually recovered, was released from hospital care and has returned to work.

## 6. SUMMARY

Veterans who served in the Persian Gulf region during Operation Desert Storm have slowly presented with chronic illnesses that produce complex signs and symptoms, such as polyarthralgia, chronic fatigue, short-term memory loss, sleep difficulties, headaches, intermittent fevers, skin rashes, diarrhea, vision problems, nausea, breathing and heart problems and other signs and symptoms that are collectively called Gulf War Syndrome or Gulf War Illnesses (GWI). Although there is not yet a case definition for GWI, the chronic signs and symptoms loosely fit the clinical criteria for Chronic Fatigue Syndrome and/or Fibromyalgia Syndrome. Some patients have additionally what appears to be neurotoxicity and brainstem dysfunction that can result in autonomic, cranial and peripheral nerve demyelination, possibly due to complex chemical exposures. Often these patients have been diagnosed with Multiple Chemical Sensitivity Syndrome (MCS) or Organophosphate-Induced Delayed Neurotoxicity (OPIDN). Chemically exposed patients can be treated by removal of offending chemicals from the patient's environment, depletion of chemicals from the patient's system and treatment of the neurotoxic signs and symptoms caused by chemical exposure(s). A rather large subset (~50%) of GWI patients have transmittible infections, including mycoplasmal and possibly other chronic bacterial infections, that have resulted in the appearance of GWI in immediate family members and civilians in the Gulf region. These infections can be treated with antibiotics, vitamin and nutritional supplementation, and in some cases, oxidative therapy. It is likely that veterans of the Gulf War who are ill with GWI owe their illnesses to a variety of exposures: (a) chemical mixtures, primarily organophosphates, antinerve agents and possibly nerve agents, (b) radiological sources, primarily depleted uranium and possibly fallout from destroyed nuclear reactors, and (c) biological sources, primarily bacteria, viruses and toxins, before, during and after the conflict. Such exposures can result in poorly defined chronic illnesses, but these illnesses can be treated if appropriate diagnoses are forthcoming.

**Acknowledgment**

The authors' studies were supported by a grant from the Rhodon Foundation for Biomedical Research, Inc. and private donations from the families of GWI patients.

## 5. REFERENCES

1. NIH Technology Assessment Workshop Panel. The Persian Gulf Experience and Health. JAMA 1994; 272: 391-396.
2. Nicolson GL, Nicolson NL. Chronic Fatigue Illness and Operation Desert Storm. J Occup Environ Med 1995; 38:14-17.
3. Haley RW, Kurt TL, Hom J. Is there a Gulf War Syndrome? Searching for syndromes by factor analysis of symptoms. JAMA 1997; 277: 215-222.
4. Murray-Leisure KA, Daniels MO, Sees J, Zangwill B, Suguitan E, Bagheri S, Brinser E, Kimber R, Kurban R, Green W. Mucocutaneous-, Intestinal-, Rheumatic Desert Syndrome (MIRDS): I. Definition histopathology, incubation period and clinical course. Intern J Med 1998; 1: 47-72.
5. Baumzweiger WE, Grove R. Brainstem-Limbic immune dysregulation in 111 Gulf War veterans: a clinical evaluation of its etiology, diagnosis and response to headache treatment. Intern J Med 1998; 1: 129-143.
6. Nicolson GL, Hyman E, Korényi-Both A, Lopez DA, Nicolson NL, Rea W, Urnovitz H. Progress on Persian Gulf War Illnesses: reality and hypotheses. Intern J Occup Med Tox 1995; 4: 365-370.
7. Nicolson GL. Chronic infections as a common etiology for many patients with Chronic Fatigue Syndrome, Fibromyalgia Syndrome and Gulf War Illnesses. Intern J Med 1998; 1: 42-46.
8. Writer JV, DeFraites RF, Brundage JF. Comparative mortality among US military personnel in the Persian Gulf region and worldwide during Operations Desert Shield and Desert Storm. JAMA 1996; 275: 118-121.
9. Kizer KW, Joseph S, Rankin JT. Unexplained illness among Persian Gulf War vetrans in an Air National Guard unit: preliminary report--August 1990-March 1995. Morb Mortal Weekly Rep 1995; 44: 443-447.
10. Eddington PG. Gassed in the Gulf. Washington D.C.: Insignia Publishing, 1997.
11. Nicolson GL, Nicolson NL. Gulf War Illnesses: complex medical, scientific and political paradox. Med Confl Surviv 1998; 14: 74-83.
12. Abou-Donia MB, Wilmarth KR. Neurotoxicity resulting from coexposure to pyridostigmine bromide, DEET and permethrin: Implications of Gulf War exposures. J Tox Environ Health 1996; 48:35-56.
13. Ziem GE. Multiple chemical sensitivity: treatment and followup with avoidance and control of chemical exposures. Toxicol Ind Health 1992; 8: 73-86.
14. Korényi-Both AL, Molnar AC, Korényi-Both AL, Fidelus-Gort RF. Al Eskan disease: Desert Storm pneumonitis. Mil Med 1992;157:452-462.
15. Magill AJ, Grogl M, Fasser RA, Wellington S, Oster CN. Viscerotropic leishmaniasis caused by *Leishmania tropica* in soldiers returning from Operation Desert Storm. N Engl J Med 1993; 328:1383-1387.
16. Nicolson GL, Nicolson NL. Diagnosis and treatment of mycoplasmal infections in Persian Gulf War Illness-CFIDS patients. Intern J Occup Med Immunol Tox 1996; 5:69-78.
17. Nicolson GL, Nicolson NL, Nasralla M. Mycoplasmal infections and Chronic Fatigue Illness (Gulf War Illness) associated with deployment to Operation Desert Storm. Intern J Med 1998; 1: 80-92.

18. U. S. Senate Committee on Banking, Housing and Urban Affairs. U. S. chemical and biological warfare-related dual use exports to Iraq and their possible impact on the health consequences of the Persian Gulf War , 103rd Congress, 2nd Session, Report: 103-900, May 25, 1994.
19. Hyman ES. A urinary marker for systemic coccal disease. Nephron 1994; 68: 314-326.
20. Nicolson GL, Nicolson NL. Doxycycline treatment and Desert Storm. JAMA 1995; 273: 618-619.
21. Nicolson GL, Nasralla M, Haier J, Nicolson NL. Diagnosis and treatment of chronic mycoplasmal infections in Fibromyalgia and Chronic Fatigue Syndromes: relationship to Gulf War Illness. Biomed Ther 1998; 16: 266-271.
22. DeFraites RF, Wanat ER, Norwood AE, Williams S, Cowan D, Callahan T. Report: Investigation of a suspected outbreak of an unknown disease among veterans of Operation Desert Shield/Storm, 123d Army Reserve Command, Fort Benjamin Harrison, Indiana, April, 1992. Epidemiology Consultant Service (EPICON), Division of Preventive Medicine, Walter Reed Army Institute of Research, Washington, DC.
23. Ferrante MA, Dolan MJ. Q fever meningoencephalitis in a soldier returning from the Persian Gulf war. Clin Infect Dis 1993; 16: 489-496.
24. Rea WJ, Pan Y, Johnson AR, Ross GH, Suyama H, Fenyves EJ. Reduction of chemical sensitivity by means of heat depuration, physical therapy and nutritional supplementation in a controlled environment. J Nutrit Environ Med 1996; 6: 141-148.
25. Nicolson GL. Considerations when undergoing treatment for chronic infections found in Chronic Fatigue Syndrome, Fibromyalgia Syndrome and Gulf War Illnesses. (Part 1). Antibiotics Recommended when indicated for treatment of Gulf War Illness/CFIDS/FMS. (Part 2). Intern J Med 1998; 1: 115-117, 123-128.

**Figure 3.** Hypothesis on the origin of some GWI. Multiple exposures (chemical, radiological, biological) or multi-factorial causes may have resulted in GWI in susceptible individuals, such as those with genetic predispositions (immune system, detoxification system, etc.)
(modified from reference 11).