

# **Gulf War Illnesses: Chemical, Biological and Radiological Exposures Resulting in Chronic Fatiguing Illnesses can be Identified and Treated**

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**SUMMARY** Gulf War Illnesses (GWI) involve multiple, complex chronic signs and symptoms that loosely fit the clinical criteria for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) and/or Fibromyalgia Syndrome (FMS). Most GWI patients had multiple exposures: (a) complex chemical mixtures, including organophosphate pesticides, anti-nerve agents, carbamates and possibly nerve and blister agents, (b) radiological sources, subjecting patients to both heavy metal and radiation effects, and (c) biological sources, including bacteria and toxins and the effects of multiple vaccines. Chemically exposed patients may benefit by removing offending chemicals and depleting toxic chemicals from the patient's system and other symptomatic treatments. Patients with systemic infections, including mycoplasmal and other chronic bacterial infections, can be treated with antibiotics and additional nutritional supplementation. Some patients may have their illness linked to radiological exposures, and a minority to battlefield stress. The vaccines are a prime suspect for immune dysfunction and chronic infections. The multiple, complex exposures resulted in poorly defined chronic illnesses, but subsets of GWI can be identified and effectively treated using appropriate procedures.

**Keywords:** Gulf War Syndrome, Fibromyalgia Syndrome, Chronic Fatigue Syndrome, chemical exposures, infections, uranium, antibiotics, vaccines, chemical and biological warfare

## **INTRODUCTION**

At least 16% (more than 100,000) of the veterans of the 1991 Persian Gulf War (PGW) slowly

(usually 6-18 months or more after the conflict) developed a variety of complex chronic signs and symptoms characterized by disabling fatigue, intermittent fevers, night sweats, arthralgias, myalgias, impairments in short-term memory, headaches, skin rashes, intermittent diarrhea and other gastrointestinal problems, respiratory complaints, photophobia and other visual disturbances, confusion, irritability, depression and other signs and symptoms (1-3). These illnesses have been called Gulf War Syndrome or Gulf War Illnesses (GWI), and they have until recently defied appropriate diagnoses (2-4). The signs and symptoms of GWI do not easily fit into ICD-9 diagnostic categories, although they loosely fall into the category of fatiguing illnesses. Routine laboratory test results are not consistent with a single, specific diagnosis (1), often resulting in veterans not receiving a diagnosis for their condition (illness of unknown origin) or receiving a diagnosis of somatoform disorder. Often the diagnoses assigned to patients reflect one or a small group of symptoms, but not the totality of the patients' complaints. GWI has been reported by various nations that deployed forces to the PGW, though the incidence of reported cases in French servicemembers is much lower than reported from other coalition nations. This last point will be discussed below.

### ***MULTIFACTORIAL ILLNESSES OF THE GULF WAR***

Although press reports often refer to illnesses associated with the PGW as Gulf War Syndrome, there is growing awareness that GWI is not a unique, new syndrome. First, all GWI patients do not have identical signs and symptoms (5,6). GWI appears to be a diverse collection of overlapping, persisting signs and symptoms from which several syndromes have been identified (3-6). Early reports found no common illness among veterans, or specific cause for GWI (1), but since then, subsets of GWI patients have been defined by several groups. Murray-Leisure et al. (7) called GWI Mucocutaneous-Intestinal-Rheumatic Desert Syndrome, and divided patients into three broad categories based on their major signs and symptoms (Table 1): (1) *mucocutaneous lesions*, (2) *intestinal disorders* and (3) *rheumatic illnesses*. Minor criteria included in these categories 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, chronic sinus or nasal congestion, atypical chest pain, new-onset asthma or chronic bronchitis, ear infections or tinnitus and dental infections.

Using factor analysis, six syndrome categories of GWI were described by Haley et al. (6) after studying a U.S. Navy Seabee (Construction Brigade) unit. The most important categories were: (4) *impaired cognition*; (5) *confusion-ataxia*; (6) *arthro-myo-neuropathy*; (7) *phobia-apraxia*; (8) *fever-adenopathy*; and (9) *weakness-incontinence*. The last three groups overlapped with groups 4 and 5, and involved weaker clustering in their analysis (6). They found that these groups differed from Post-Traumatic Stress Disorder (PTSD), depression, somatoform disorder and malingering (6). Psychological disorders such as PTSD have been diagnosed in PGW veterans (8), but this likely accounts for only a minor fraction of GWI cases. A recent psychiatric analysis indicates that the majority of GWI cases do not meet PTSD criteria (9).

Baumzweiger and Grove (10) have described GWI as *neuro-immune disorders* that involve the central, peripheral and autonomic nervous system and immune system. They attribute a major source of illness to brainstem damage and central, peripheral and cranial nerve dysfunction with demyelination. They found GWI patients to have muscle spasms, memory and attention deficits, ataxia and increased muscle tone (10).

Alternative diagnoses have been proposed for certain subsets of GWI. Some patients may have suffered sand inhalation resulting in a chronic pulmonary condition (pneumonitis) that has been called Al Eskan disease (11). GWI patients can also have chronic bacterial and viral infections as an important source of morbidity (12).

The illnesses collectively called GWI are usually not fatal (13); however, thousands of

PGW veterans have died since the war (14). Possible reasons why these deaths have not been evaluated in official studies may be the limited populations studied, and lack of information on PGW veterans who left the Armed Forces, and died outside of military and VA hospitals (15). Estimates of between 15,000 and 25,000 or more deceased US veterans have been advanced, but the exact figures are unknown. Therefore, it is difficult to determine if PGW veterans are at higher risk of death than non-deployed personnel. Three groups have shown, however, that PGW veterans do have increased rates of accidental deaths compared to non-veterans (16-18). It has been postulated but not proven that this is due to neurologic impairments affecting the operation of motor vehicles.

It is claimed that there are no unique illnesses associated with deployment to the PGW<sup>1</sup>-similar illness clusters (at lower rates) can be found in non-PGW veterans deployed to Bosnia (19,20). Epidemiologic analyses of GWI have been criticized on the basis of self-reporting and self-selection, and that the veterans under study may not be representative of the larger population of veterans (19). Those criticisms notwithstanding, it remains important to characterize signs and symptoms and identify exposures, if possible, of PGW veterans in order to find effective treatments for specific subsets of GWI patients.

Most current case definitions for GWI are symptom-based, and a consensus of different researchers has shown much higher prevalence rates of GWI in deployed than in non-deployed forces. One case control study of PGW veterans showed higher symptom prevalence in the deployed group than in personnel from the same units that were not deployed to the PGW (21). For certain signs and symptoms, this difference was dramatic (for example, the rate of diarrhea in the deployed group was over 13-times greater than in the non-deployed group) (21). Steele (4) showed that in three studies, PGW-deployed forces had excess rates of 26%, 30% and 32% of GWI symptom patterns (defined as % of cases meeting the GWI case definition in deployed forces minus % of cases meeting GWI case definition in non-deployed forces). Although it has been argued that the arthralgias, fatigue, memory loss, rashes and diarrhea found in GWI patients are nonspecific and often lack a physical cause (19), this conclusion may simply be the result of inadequate workup and lack of availability of routine tests that could define the underlying organic etiologies for these conditions.

### ***SIMILARITY OF GWI TO CFS/ME AND FMS***

In most GWI patients the variable incubation time, ranging from months to years after presumed exposure, the cyclic nature of the relapsing fevers and the other chronic signs and symptoms and their subsequent appearance in immediate family members are consistent with an organic, likely infectious process, not a psychosomatic disease or somatoform disorder (2,3,6,7). The syndromes most similar to GWI are Chronic Fatigue Syndrome (CFS) (or Myalgic Encephalomyelitis, ME) and Fibromyalgia Syndrome (FMS) (2,22). 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 abnormalities and a variety of other responses that result in a CFS/ME- or FMS-like disorder (22,23). CFS/ME is defined by persistent, debilitating fatigue 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. Patients also report at least four of the following symptoms: fever, sore throat, arthralgia, myalgia, headaches, painful lymph nodes, sleep difficulties, and neuropsychiatric complaints, such as memory loss, visual disturbances, confusion, irritability and depression (24). These signs and symptoms closely parallel those found in most cases of GWI (2,22-24). This also indicates that GWI is not a new syndrome, and it has close similarities to CFS/ME.

There are some differences between GWI and CFS/ME/FMS that may be important. Haley et al. (6) and Baumzweiger and Grove (10) have stressed that unlike most cases of

CFS/ME and FMS, some cases of GWI are associated with ataxia and increased motor tone. They speculated that this may reflect cranial and peripheral nerve demyelination, brainstem inflammation, and/or limbic system involvement. Using proton magnetic resonance to measure the ratio of plasma homovanillic acid and 3-methoxy-4-hydroxyphenylglycol Haley et al. (25) found reductions in the left basal ganglia dopamine production, supporting the theory that injury to dopaminergic neurons in the basal ganglia can occur in GWI.

### ***CHEMICAL EXPOSURES AND GWI***

The overlapping chronic signs and symptoms found in GWI patients could be caused by quite different types of exposures. PGW participants were exposed to chemical, radiological and/or biological agents, and most report combinations of such exposures (Figure 1) (3,6,7,10,14,23,26). Accurate diagnosis and successful treatment of GWI subsets will depend on identifying the illness-provoking exposures, because the different exposures require different methods for amelioration (22,23).

PGW veterans were exposed to a variety of chemicals, including insecticides, such as the insect repellent N,N-dimethyl-m-toluamide, the insecticide permethrin and other organophosphates, fumes and smoke from burning oil wells, 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 (23). Some CW exposure may have occurred because of destruction of CW stores in factories and storage bunkers during and after the war as well as possible offensive use of CW agents (14,27). Some feel that there was no credible evidence for CW exposure (19); however, many veterans have been notified by the Department of Defense of possible CW exposures.

Exposures to mixtures of toxic chemicals can result in chronic illnesses, even if the exposures are at low-levels (6,10,23,27). Such exposures can cause a wide variety of signs and symptoms, including chronic neurotoxicity and immune suppression. Abou-Donia and Wilmarth (28) found that combinations of 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. Similarly, Moss (29) found that mixtures of chemicals similar to those encountered by PGW veterans were much more toxic than the sum of the individual chemicals' toxicity. Although low levels of individual organophosphate chemicals may not cause signs and symptoms in exposed, non-deployed civilian workers (30), this does not negate a causal role of multiple chemical exposures in causing chronic illnesses such as GWI (19). Organophosphate-Induced Delayed Neurotoxicity (OPIDN) is an example of chronic illness that may be caused by multiple, low level chemical exposures (Figure 1) (31). Multiple Chemical Sensitivity Syndrome (MCS) has also been proposed to result from multiple low level chemical exposures (32). These syndromes can present with many of the signs and symptoms found in GWI patients, and many GWI cases may eventually be explained by complex chemical exposures (6,23,25,29-33). In chemically exposed GWI patients, memory loss, headaches, cognitive problems, severe depression, loss of concentration, vision and balance problems and chemical sensitivities, among others, typify the types of signs and symptoms characteristic of organophosphate exposures. Arguments have been advanced that such exposures do not explain GWI, or that they may only be useful for a small subset of GWI patients (19). These arguments for the most part are based on the effects of single agent exposures (19), not the multiple, complex exposures that were encountered by PGW veterans (33). Since it is unlikely that one or even a few exposures will explain all the signs and symptoms found in GWI patients, seeking subsets or clusters of exposed patients may not be as limiting as suggested by Sartin (19). It could eventually allow practitioners to use unique combinations of treatments based on individual exposures of PGW veterans.

The onset of signs and symptoms of GWI for most patients was between six months and

two years or more after the end of the war. Slow onset of clinical signs and symptoms in chemically exposed individuals is not unusual for OPIDN (34). Since low-level exposure to organophosphates was common in U.S. PGW veterans, the appearance of delayed, chronic signs and symptoms similar to OPIDN could have been caused by multiple low-level exposures to pesticides, nerve agents, anti-nerve agents and/or other organophosphates (27-29,32), especially in certain subsets of GWI patients (6).

CW agents were also present in the Persian Gulf region from the bombing of CW factories and storage facilities (and their demolition after the war), and the possible offensive use of CW delivered by SCUD B (SS1) missiles, aircraft or vehicles outfitted with CW sprayers, artillery shells and rockets, CW mines and other sources (23,27,31). Iraqi Armed Forces were known to have extensive stores of such weapons, and intelligence reports indicated that orders to use offensive CW agents were given. In testimony to the U. S. Congress, Army officers indicated that over 14,000 CW alarms sounded during but not before or after the air/ground offensive, and some soldiers were given medals for identifying the types of CW that were released (35). 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 region, and an unknown quantity of these weapons were released into the atmosphere during the air campaign and by the destruction of Iraqi storage bunkers after the conflict (22,35). That low level exposure to nerve agents combined with anti-nerve agents plus other organophosphate exposures may have resulted in delayed casualties in at least some subsets of GWI is a possibility that should not be casually dismissed (19).

### ***RADIOLOGICAL EXPOSURES AND GWI***

Depleted uranium (DU) was used extensively in the Gulf War, and it remains an important contaminant of the battlefield (14). DU, a by-product of uranium processing, is used in armor-penetrating ammunition and in protective armor on tanks and other vehicles. DU had been thought to contain only uranium isotopes, primarily  $^{238}\text{U}$  (greater than 99%), and small amounts of  $^{235}\text{U}$  and  $^{234}\text{U}$ . However, when DU was analyzed, it was found to contain small quantities of plutonium and other isotopes, which are much more toxic and radioactive than DU itself (36). When a DU penetrator hits an armored target, it ignites, and between 10% and 70% of the shell aerosolizes, forming uranium oxide particles (36). The particles that form are usually small (less than 5  $\mu\text{m}$  in diameter) and due to their high density settle quickly onto vehicles, bunkers and the surrounding sand, where they can be easily inhaled, ingested or re-aerosolized.

Following contamination, the organs where DU can be found include the lungs and regional lymph nodes, kidney and bone. However, the Armed Forces Radiological Research Institute (AFRRI) also found DU in blood, liver, spleen and brain of rats injected with DU pellets (37). Pregnant rats transmitted DU to placental and fetal tissues as well. Researchers at the AFRRI further noted that "cells exposed to DU are transformed to tumorigenic cells in immune-compromised mice" (37). It is therefore possible that the immune-compromising effects of DU itself or other PGW exposures have led to DU inducing cancer in PGW veterans, and also that DU has produced adverse fetal effects. Studies on DU carriage should be initiated as soon as possible, to determine the prevalence of contamination, and extent of body stores of uranium and other radioactive heavy metals.

Procedures have been developed for analysis of DU metal fragments (38) and DU in urine (39). However, urine testing does not detect uranium in all body sites (36). So far, analysis of DU-contaminated PGW veterans has not shown them to have severe signs and symptoms of GWI (39), but few PGW veterans have been studied. Allegations that DU has led to leukemia in European troops serving in Kosovo (of whom 17 have died from leukemia) and Bosnia are being taken seriously. NATO has called for testing troops from all 19 NATO members for DU (36). In January 2001 the European Parliament called for an end to the use of all DU ammunition by

NATO (36).

### ***OTHER ENVIRONMENTAL EXPOSURES AND GWI***

In addition to the chemicals (and fumes from diesel-powered heaters) in tents and surrounding areas, soldiers were exposed to burning oil well fires and ruptured petroleum pipelines as well as fine, blowing sand. The small size of sand particles ( $\ll 0.1$  mm) and the relatively constant winds in the region probably resulted in some sand inhalation. The presence of small sand particles deep in the lungs can produce a pulmonary inflammatory disorder that can progress to pneumonitis or Al-Eskan Disease (11,40). Al-Eskan disease, characterized by reactive airways, usually presents as a pneumonitis that can eventually progress to pulmonary fibrosis, and possibly immunosuppression followed by opportunistic infections. Although it is doubtful that many GWI patients have Al-Eskan Disease, the presence of silica-induced immune suppression in some soldiers could have contributed to persisting opportunistic infections in these patients (12,14,22,27).

### ***BIOLOGICAL EXPOSURES AND GWI***

A small number of PGW veterans had confirmed infections with parasites, such as Malaria, Leishmaniasis and Schistosomiasis. These infections could be the cause of illnesses in additional veterans (7). Although these diagnoses may be difficult and are often not considered, characteristic signs and symptoms occur in these illnesses, and diagnostic tests are available. Infection by *Leishmania tropica*, spread by the sandfly *Phlebotomus papatasi*, can result in viscerotropic Leishmaniasis, fever, lymphadenopathy and hepatosplenomegaly (41). The prevalence of Leishmaniasis has been estimated at fewer than 100 cases in PGW veterans.

Biological toxins were also present in the Kuwaiti Theater of Operations (23,27,42). The Iraqi Army had offensive stores of aflatoxin (*Aspergillus flavus* toxin), ricin (from *Ricinus communis* beans), *Clostridium botulinum* toxin and tricothecene mycotoxins produced by various species of fungi. Some of these toxins can be fatal in very low doses. Aflatoxin can cause delayed carcinogenic or immunosuppressive effects.

Bacterial infections are suspected in many GWI patients (12,22,23). Murray-Leisure et al. (7) have described a subset of GWI associated with cutaneous sand exposure. The illness may be caused by a transmissible agent found in sand that is endemic to the region. The risk for sand-associated illness appeared to be highest in the fall. Although no sand-associated agent has so far been identified, the slow development of the same signs and symptoms in spouses and children of veterans with GWI suggests that a slow-growing microorganism has been transferred.

Polymerase chain reaction (PCR) evidence for transmissible infectious agents has been found in GWI patients. In many cases, the veterans' immediate family members appear to have later developed similar signs and symptoms (43-45). One estimate derived from inquiries of over 1,200 GWI families indicated that approximately 77% of spouses and 65% of children born to affected veterans after the war now have the signs and symptoms of GWI (46). Not every family member developed a GWI-like illness, but those that did had similar signs and symptoms and similar PCR evidence of infection. Because of the apparent slow rate of transmission to immediate family members, the general public is probably not at high risk for contracting GWI from casual contact with GWI patients. However, health care personnel may be at some risk.

Evidence for infectious agents has been found in GWI patients' urine (14) and blood (22,43-45). Hyman (47) has used a microscopic technique to identify remnants of bacterial cell walls in urine, and he has successfully treated patients with several courses of broad spectrum antibiotics. We (43-45,48) and others (49) have found that most of the signs and symptoms in a large subset of GWI patients can be explained by chronic pathogenic bacterial infections, such as

mycoplasmal infections. In studies of over 1,500 U.S. and British veterans with GWI, approximately 40% of GWI patients have PCR evidence of such infections, compared to 6-9% in the non-deployed, healthy population (43). This has been confirmed in a large study of 1,600 veterans at over 30 VA and DoD medical centers (VA Cooperative Clinical Study Program #475). Historically, mycoplasmal infections were thought to produce relatively mild diseases limited to particular tissues or organs, such as urinary tract or respiratory system (22,43). However, the mycoplasmas detected in GWI patients with molecular techniques, such as *Mycoplasma fermentans*, are highly virulent, colonize a wide variety of organs and tissues, and are difficult to treat (43,50). The mycoplasma most commonly detected in GWI, *Mycoplasma fermentans* (found in >80% of those GWI patients positive for any mycoplasma), is found intracellularly. It is unlikely that this type of infection will result in a strong antibody response, which may explain the lack of serologic evidence for these types of intracellular infections (51).

When civilian patients with CSF/ME or FMS were similarly examined for systemic mycoplasmal infections about 50% of these patients were positive, indicating another link between these disorders (43). In contrast to GWI, however, several species of mycoplasmas other than *M. fermentans* were found in higher percentages of CSF/ME and FMS patients than GWI patients (43,49,52).

Approximately one-half of GWI patients also show fragile chromosomes that are more easily degraded by cellular nucleases, resulting in release of characteristic nucleotide fragments (53), but this might be due to the action of intracellular bacteria that are known to release chromosome-damaging chemicals (50,54). Similarly, the finding of activation of the coagulation system in GWI patients could also be related to chronic infections that cause coagulation disturbances (55).

A few other chronic infections have been found in GWI patients. In contrast to an early official report (56), we have found preliminary evidence for *Brucella* infections in some GWI cases. Inhalation of *Brucella melitensis* can cause many but not all of the signs and symptoms of GWI. Another bacterial infection found in small numbers of cases includes Q Fever (57), caused by *Coxiella burnetii*.

### **MULTIPLE VACCINES AND GWI**

A possible source for immune disturbances and chronic infections found in GWI patients is the multiple vaccines that were administered close together around the time of deployment to the Gulf. Unwin et al. (20) and Cherry et al. (58) found a strong association between GWI and the multiple (including biological warfare) vaccines that were administered to British PGW veterans. Unwin et al. (20) and Goss Gilroy (59) also noted an association specifically with anthrax vaccines and GWI symptoms in British and Canadian veterans. Steele (4) found a three-fold increased incidence of GWI in *nondeployed* veterans from Kansas who had been vaccinated in preparation for deployment, compared to non-deployed, non-vaccinated veterans. Mahan et al. (26) found a two-fold increased incidence of GWI symptoms in U.S. veterans who recalled they had received anthrax vaccinations at the time of the Gulf War, versus those who thought they had not.

In the United States, GWI signs and symptoms have developed in personnel who recently received the anthrax vaccine. On some military bases this has resulted in chronic illnesses in as many as 7-10% of personnel receiving the vaccine (60). The chronic signs and symptoms associated with anthrax vaccination are similar, if not identical, to those found in GWI patients, suggesting that at least some of the chronic illnesses suffered by veterans of the PGW were caused by vaccines (60). Undetectable microorganism contaminants in vaccines could have resulted in illness, and may have been more likely to do so in those with compromised immune systems. This could include individuals with DU or chemical exposures, or personnel who

received multiple vaccines in a short period of time. Since contamination with mycoplasmas has been found in commercial vaccines (61), the vaccines used in the PGW should be considered as a possible source of the chronic infections found in GWI (60).

### ***TREATMENT OF GWI***

Treatment of GWI should follow from knowledge of the types of exposures encountered around the time of the PGW. For example, the treatment of chemically sensitive patients involves removal of offending chemicals from the patients' environment, and may also include methods to remove chemicals from the patients' depot sites, and other treatments (23,62-65). Chemically exposed patients can be extremely sensitive to a variety of commonly encountered chemicals, including perfumes and air fresheners, petrochemical fumes, chlorine, cleaning solutions and solvents. They may also be very sensitive to certain foods, and special diets can be necessary. In some cases, cutaneous contact with certain substances can cause strong reactions.

GWI patients with MCS or OPIDN may benefit from dry saunas (63), as well as magnesium sulfate-hydrogen peroxide baths (66). Toxic substances may be removed through a program of heat depuration, physical therapy, nutritional supplementation, and in some cases other therapies might be employed (62-65). In addition to heat, exercise and diet, a variety of medications may alleviate some symptoms in GWI patients. Some patients have benefited from anti-anxiety, anti-depressant and anti-inflammatory drugs (10), but this may not be beneficial for other GWI patients, especially those with chronic infections (22,63) or with MCS.

Amelioration of DU carriage depends on reducing the body burden of heavy metals by chelation, and surgical removal of shrapnel, combined with nutritional strategies. However, it must be recognized that the actual composition of DU and the extent of its toxicity remain to be determined. The extent of troop contamination also remains unknown and should be determined. Although chelation therapy has been proposed for DU contamination, the effectiveness of chelation for DU removal is uncertain, particularly for exposures that took place years earlier.

Chronic infections can be treated with the appropriate antibiotics. Treatment with antibiotics can result in improvement and even recovery in patients made ill by bacteria or mycoplasmas, such as *M. fermentans* (22,43-45). The recommended treatments for systemic mycoplasmal infections require long-term antibiotic therapy (22), because few patients recover after only a few weeks or months of treatment. This may be a reflection of the intracellular locations of most mycoplasma, the slow-growing nature of these microorganisms, or their inherent resistance to antibiotics (50). Once our patients recovered and were able to return to pre-illness levels of activity, mycoplasma gene sequences could no longer be detected in their leukocytes. These clinical responses were not due to placebo effects, because administration of antibiotics that are not effective against mycoplasmal infections, such as penicillins, resulted in patients becoming more, not less, symptomatic. Interestingly, CFS/ME, FMS and GWI patients with systemic infections that slowly recover on antibiotic therapy become less environmentally sensitive, suggesting that their immune systems may be returning to pre-illness states. If such patients had illnesses that were caused by stress or solely by chemical exposures, they would not respond to the recommended antibiotics and slowly recover. In addition, if such treatments were just suppressing autoimmune activity, then patients should have relapsed after the treatments were discontinued (50).

We and others (67) have found abnormal levels of certain substances (thyroid hormone, aldosterone, cortisol, vitamin B12) in some PGW patients, possibly due to autoimmune attack on endocrine tissues. These levels should be monitored and appropriately supplemented.

### ***FINAL COMMENTS ON GWI***

Because of the relatively nondescript, widespread, chronic signs and symptoms of GWI, it has defied a simple case definition. Various authors have described GWI as a set of distinct syndromes. However, GWI may simply be a complex collection of overlapping chronic illnesses caused by multiple toxic chemical, radiological and biological exposures, including vaccines.

Interestingly, the French Ministry of Defense reported very few GWI cases (68). During the PGW the French forces did not use vaccines as a primary defense against Iraqi BW, and they did not use anti-nerve agents extensively as a defense against Iraqi CW agents (69). Instead, they used controlled environments, prophylactic antibiotics to counter BW agents, and depended on protective suits to counter CW agents (27,60,69). Finally, efforts are being made to determine the relative effectiveness of these very different chemical and biological prophylactic and treatment strategies used by different nations (69). And the French Ministry of Defense has been urged to investigate the role of vaccinations, obtained by small numbers of French troops while serving with US and British forces, in French soldiers who have now developed GWI (60,68).

Recent attention to the role of chemical and radiological exposures, hormonal deficiencies, and infections with microorganisms (some possibly originating from the vaccines used in the PGW), in GWI patient subsets, has allowed investigators to successfully treat GWI cases. Because this approach to GWI has not been widely used, we hope to encourage other clinicians to extensively evaluate and successfully treat ill PGW veterans and their families.

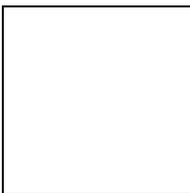
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**Figure 1.** Hypothesis on how multiple toxic exposures, including multiple vaccines (2), chemical (3), radiological and biological (4) exposures, may have resulted in GWI in predisposed, susceptible individuals (1) [modified from Nicolson et al.(23)].

**Table 1.** Proposed Gulf War Illness patient subsets.

Subset or Cohort	Major Signs/Symptoms	Reference (No.)
Mucocutaneous disorders	pustular dermatitis, other signs	Murray-Leisure et al. (7)
Intestinal disorders	IBS, diarrhea, other signs	Murray-Leisure et al. (7)
Rheumatic Illnesses	polyarthralgias, night sweats, etc.	Murray-Leisure et al. (7)
Impaired cognition	attention, memory, reasoning, insomnia, fatigue, depression and headaches	Haley et al. (6)
Confusion-ataxia	confusion, reasoning, disorientation, balance, depression, vertigo and impotence	Haley et al. (6)
Artho-myo-neuropathy	polyarthralgias and myalgias, fatigue, muscle fatigue, extremity paresthesias	Haley et al. (6)
Phobia-aproxia	numbness, nausea, dizziness, tingling sensations, other signs	Haley et al. (6)
Fever-Adenopathy	intermittent fever, lymphadenopathy other signs	Haley et al. (6)
Weakness-incontinence	muscle weakness, dyspareunia, incontinence, other signs	Haley et al. (6)
Neuro-immune	memory, attention, ataxia other signs	Baumzweiger and Grove(10)
PTSD	stress, depression, somatoform	Engel et al. (8)
Al-Eskan disease	pneumonitis, other signs	Korényi-Both et al.(11,40)
Chronic infections	polyarthralgias, night sweats, myalgias, other signs	Nicolson (12) Nicolson et al.(43-45)