

Gulf War Illnesses: Complex Medical and Scientific and Political Paradox*

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Gulf War Illnesses are a collection of disorders that for the most part can be diagnosed and treated, if effective programs exist to assist veterans and in some cases their immediate family members. Although these illnesses are complex and have multi-organ signs and symptoms, a rather large proportion of these patients can be identified as having Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) and/or Fibromyalgia Syndrome (FMS). Although there are many possible causes of CFS/ME/FMS, including chronic chemical exposures, chronic infections can explain, at least a subset of patients, the apparent transmission of these illnesses to immediate family members and the appearance of multi-organ chronic and autoimmune signs and symptoms. Unfortunately, many veterans who have been diagnosed with chronic infections, such as mycoplasmal and other bacterial infections, cannot obtain adequate treatment for their conditions, resulting in their reliance on private physicians and clinics for assistance. This lack of prompt response may be responsible for the slow transmission of the illness to non-veterans.

KEYWORDS: Chemical and Biological Warfare, Gulf War Syndrome, Operation Desert Storm, Chronic Infections

Gulf War Syndrome or Gulf War Illnesses (GWI) are characterized by their complex, multi-organ, chronic signs and symptoms, including neurological, musculo-skeletal, rheumatic, mucocutaneous, gastrointestinal, sinopulmonary, and constitutional, among others.¹ On the basis of complex multiorgan signs and symptoms GWI has been called Mucocutaneous-Intestinal-Rheumatic Desert Syndrome by Murray-Leisure *et al.*² Also included in this complex clinical picture are increased sensitivities to various environmental agents and chemicals and enhanced allergic responses.³ Often such patients have cognitive problems and are seen by psychologists or psychiatrists who usually decide in the absence of contrary laboratory findings that their condition is a stress-induced somatoform disorder, such as Post-Traumatic Stress Disorder (PTSD).³ Alternatively, these patients receive an 'unknown' diagnosis, making it extremely difficult for them to receive adequate care and compensation. However, there is another, quite different possibility--these patients may suffer from chronic chemical exposure and/or chronic infections that can penetrate the central and peripheral nervous systems as well as other tissues and organs and cause the complex signs and symptoms similar to those seen in Chronic Fatigue Syndrome (CFS) and Fibromyalgia Syndrome (FMS), including immune dysfunction, that may underlie some of the environmental responses.⁵⁻⁷

A Multifactorial Illness

Our hypothesis (Figure 1) is that GWI is not caused by stress or psychological problems, but by multiple exposures to chemical, environmental, radiological and/or biological exposures resulting in chronic multi-system signs and symptoms that for the most part can be diagnosed as existing diseases or syndromes.⁵⁻⁷ We have been particularly interested in veterans with GWI whose family members are now also sick with similar signs and symptoms, suggesting that many GWI patients may suffer from biological, not chemical or radiological origins for their illnesses. Illnesses caused by chemical or radiological exposures should not be transmitted to family members. The occurrence of GWI in immediate family members is officially denied by the U.S. Departments of Defense (DoD) and Veterans' Affairs (DVA)

Figure 1

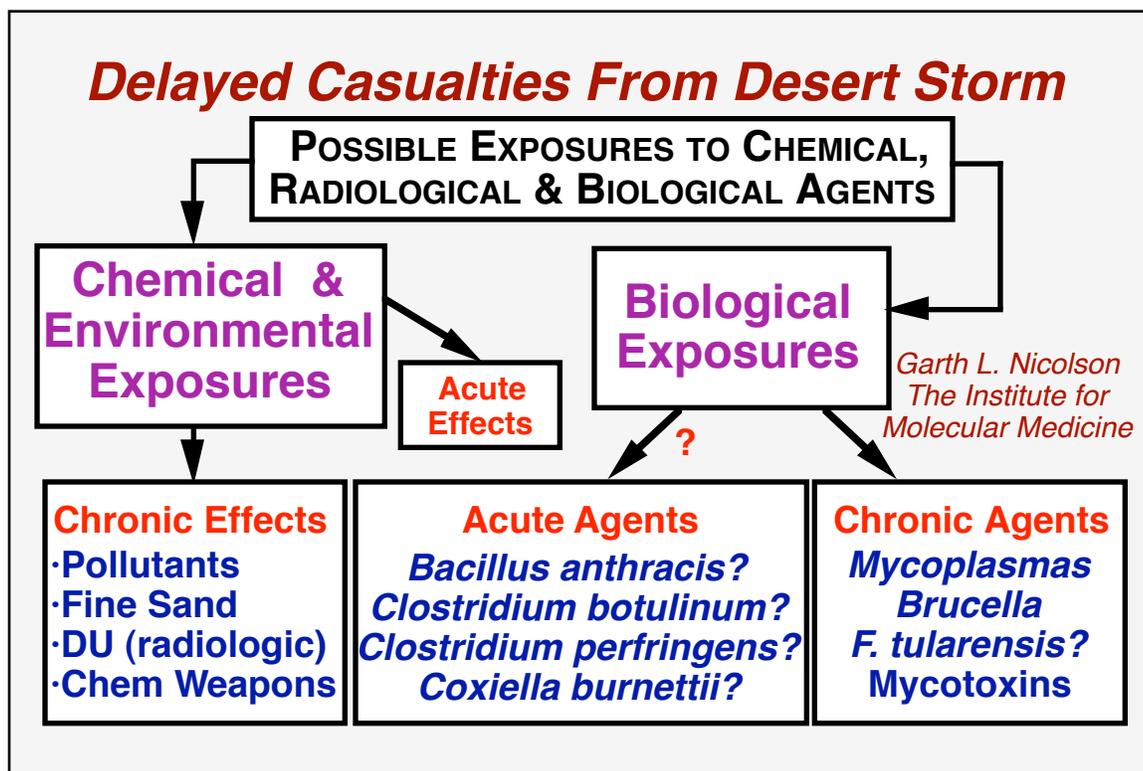


Figure 1. Multifactorial causes of Gulf War Illnesses. Explanation for the delayed appearance of Gulf War Illnesses in personnel deployed to the Persian Gulf during Operation Desert Storm. In the figure personnel were exposed to a variety of environmental, chemical and biological agents.

and in the U.K. by the Ministry of Defense (MoD). Although some family members with the same complex signs and symptoms could have developed their illnesses by contact with war souvenirs, packs or uniforms, only biological causes of GWI can account for the overwhelming fraction of family members contracting the same apparent illness in this important subset of GWI patients. Our research into GWI and the laboratory tests for GWI-associated pathogens that we developed have been done completely without compensation or funding from the United States Government. Since our Institute for Molecular Medicine is a not-for-profit private research institute dedicated to discovering new diagnostic and therapeutic solutions for chronic human diseases, we do not charge veterans or their family members for our assistance and services. In fact, we are assisting without compensation 'Desert Storm' veterans from other coalition countries that also have GWI casualties.

In addition to an unknown number of veterans' immediate family members with GWI, over 100,000 Desert Storm veterans are experiencing a variety of chronic signs and symptoms characterized by disabling fatigue, intermittent fever, joint and muscle pain, impairment of short-term memory, headaches, skin rashes, diarrhea, vision and gastrointestinal problems and a collection of additional signs and symptoms that has defied a classical clinical case definition.⁴ These chronic signs and symptoms usually do not progress to cause death, hence the lack of evidence for increased mortality rates,⁸ but nonetheless there are now thousands of Desert Storm veterans dead for a variety of reasons.³ Part of the confusion in diagnosing GWI is that somewhat similar or overlapping signs and symptoms can be caused by quite different types of exposures (chemical, radiological or biological or more likely combinations of these).

The diagnosis and successful treatment of GWI depend on identifying the underlying exposures involved, because these illnesses are treated differently if their origins are chemical, radiological or biological. For the most part, GWI signs and symptoms began to present from six months to one year or more after the

end of Operation Desert Storm, and when immediate family members present with the same illness, their onset usually occurred from six months to one year or more after the onset of the veterans' illness; not every family member always develops GWI. The U.S. Senate investigated the issue of transmission of GWI by surveying immediate family members; they found in 1994 after surveying over 1,000 veterans' families that approximately 77% of spouses and approximately 65% of children were complaining of similar health problems as GWI patients.⁹ Because of the apparent slow rate of transmission of GWI to immediate family members, we do not feel that the general public is at high risk for contracting GWI from casual contact with GWI patients; however, there is likely to be some exposure risk associated with prolonged, close contact in restricted quarters.

Caring for Gulf War Illnesses

The DoD has claimed from their clinical evaluation program that Gulf War veterans do not show higher rates of health problems than the U.S. population as a whole. They failed to mention, however, that all U.S. personnel that served in the Gulf received health clearances before they were deployed, and yet many returned with illnesses or later developed illnesses that cannot be explained. National Guard and Air Force Reserve units were studied by the Center for Disease Control (CDC) in Atlanta for evidence of chronic health problems associated with deployment to the Persian Gulf, and it is clear from this CDC study that the Persian Gulf deployed soldiers have much higher frequencies (from 2.5-times to 13.5-times higher) of chronic health problems (more than 6 months' duration) than those who were not deployed to the Persian Gulf Theater of Operations.¹⁰

A major problem for Gulf War veterans with GWI has been obtaining adequate care for their illnesses. Unfortunately, the signs and symptoms of GWI are not well established as criteria for particular diseases treated by the DoD or DVA. Indeed, most GWI patients do not readily fit into DoD or VA diagnosis categories, resulting in many veterans receiving 'unknown' or PTSD diagnoses. Although stress can exacerbate clinical conditions, we felt it unlikely that the complex signs and symptoms of GWI that veterans displayed (and especially those where immediate family members have similar signs and symptoms) were due to PTSD. When we studied 650 veterans of Operation Desert Storm and their immediate family members who suffer from GWI, we found that their multiple chronic signs and symptoms were very similar to patients with CFS (often called Chronic Fatigue-Immune Dysfunction Syndrome [CFIDS] or Myalgic Encephalomyelitis [ME]) and/or Fibromyalgia Syndrome (FMS).^{2-4,6} Although these chronic conditions can have stress as an exacerbating factor, they are extremely unlikely to be solely caused by stress or psychiatric problems. In addition, the fact that many immediate family members have also presented with similar signs and symptoms indicates that diagnoses based on PTSD may be a gross oversimplification of GWI patients. The variable incubation time of GWI, ranging from months to years after presumed exposure, the cyclic nature of the relapsing fevers and other signs and symptoms, and the types of signs and symptoms are consistent with diseases caused by combinations of agents (Figure 1).

The Role of Infection

We suggested that GWI/CFS/ME/FMS can be explained in many patients by exposure of veterans to various biological agents (chronic pathogenic infections) in combination with chemical exposures and in veterans' family members to biological agents transported back home by the veterans (Figure 1).¹¹ To confirm or eliminate the possibility that chronic infections are an important factor in GWI, and especially in immediate family members with GWI, we began by examining a variety of biological agents (bacteria, viruses, and others) that can cause the chronic, overlapping, system-wide signs and symptoms seen in GWI. We could exclude most of the acute or fast acting bacteria (listed in Figure 1), because of the chronic nature of GWI and the slow appearance and nature of signs and symptoms. After examining GWI patients' blood for the presence of chronic biological agents, the most common infection found was an unusual microorganism, *Mycoplasma fermentans* (incognitus strain), a slow-growing mycoplasma located deep inside blood leukocytes (white blood cells) and tissues of slightly under one-half of GWI patients studied.^{11, 12} This microorganism is similar to a bacterium without a cell wall, and although mycoplasmas are often found at superficial sites in humans, such as in the oral cavity, they are rarely found in the blood. When they are in the blood, similar to other bacteria, they can cause a dangerous

system-wide or systemic infection.¹³ In addition, cell-penetrating mycoplasmas, such as *Mycoplasma fermentans*, may produce unusual autoimmune-like signs and symptoms when they escape from nerve and other cell types and stimulate host immune responses to host cell antigens carried on the mycoplasma surface. Our detection of mycoplasmal infections in the blood leukocytes of ~45% of the GWI patients examined (76 out of 170 patients), including 4 out of 6 British Desert Storm veterans with GWI, indicate that systemic infections may be a major contributor to GWI.^{11,12}

In response to our published studies^{11,12} and formal lectures at the DoD (in 1994 and 1996) and DVA (in 1995), Dr. Steven Joseph, then Assistant Secretary of Defense for Health Affairs, and Dr. Kenneth Kizer, Undersecretary for Health, DVA, stated in letters to the press and various members of the U.S. Congress that this type of infection is commonly found, not dangerous and not even a human pathogen, and our results have not been duplicated by other laboratories. These statements could not be further from the truth. The Uniformed Services University of the Health Sciences, the U.S. military's medical school, has been teaching its medical students for years that this type of infection, although rare in the U.S. civilian population, is very dangerous and can progress to system-wide organ failure and death.¹⁴ In addition, the Armed Forces Institute of Pathology (AFIP) has been publishing for years that this type of infection can result in a fulminant infection that results in death in nonhuman primates¹⁵ and in man.¹⁶ The AFIP has also suggested treating patients with this type of infection with doxycycline,¹⁷ one of the antibiotics that we have recommended.¹¹⁻¹² So why has the DVA issued guidelines stating that GWI patients should not be treated with antibiotics like doxycycline, even though in a significant number of patients it has been shown to be beneficial? In response to the comments that our tests have not been duplicated, a certified diagnostic clinical laboratory, Immunosciences Laboratories of Beverly Hills, CA, has been conducting diagnostic tests on mycoplasmal infections in blood of GWI and CFS/ME patients, and they are finding essentially the same results as us. Thus our results have been replicated by a certified commercial laboratory. The DoD and DVA have also claimed that we have not cooperated with them or the CDC in studying this problem. This is not true. In fact, as stated above we have lectured to the DoD and DVA on several occasions on this subject, and we formally invited DoD and DVA scientists and physicians to the Institute for Molecular Medicine to learn our diagnostic procedures. We recently received a contract (DAMD17-97-M-1452) from the DoD to train their scientists in the types of procedures that we used to diagnose chronic infections in GWI patients. We have done everything possible to co-operate with the DoD, DVA and CDC on this problem, and we even published a letter in the *Washington Post* on 25 January 1997 indicating that we have done everything possible to co-operate with government agencies on GWI issues. We formally invited DoD and DVA scientists and physicians to the Institute for Molecular Medicine to learn our diagnostic procedures on 23 December 1996 at a meeting convened at Walter Reed Army Medical Center by Major General Leslie Burger at the request of Congressman Norman Kicks (Democrat-Washington). We have been and are fully prepared to share our data and procedures with government scientists and physicians. Although government laboratories can test for mycoplasmal infections and been conducting their own examination of mycoplasmal infections in GWI patients, they are using relatively insensitive, outdated antibody tests or conventional molecular biological tests, and we would not expect them to detect the infection by these procedures.

Antibiotic Therapy of GWI

In GWI patients that tested positive for mycoplasmal infections in their blood, we have found that they can be successfully treated with multiple 6-week courses of specific antibiotics, such as doxycycline (200-300 mg/day), ciprofloxacin (or Cipro, 1500 mg/day), azithromycin (or Zithromax, 500 mg/day), clarithromycin (or Biaxin, 500-1000 mg/day) or minocycline (200-300 mg/day),^{11, 12} with nutritional and immune support. Multiple treatment cycles are required, and patients relapse often after the first few cycles, but subsequent relapses are milder and patients eventually recover.¹² Using the techniques of Nucleoprotein Gene Tracking¹⁸ and forensic Polymerase Chain Reaction, approximately 45% of the Desert Storm veterans and their immediate family members with GWI/CFS/ME signs and symptoms in our studies showed evidence of mycoplasmal infections in their blood leukocytes.¹¹⁻¹² In contrast, in nondeployed, healthy adults the incidence of mycoplasma-positive tests were less than 5%.¹² We stress that these studies do not involve controlled patient populations, such as all veterans that served in a single unit compared to similar numbers of nondeployed personnel from the same unit; therefore, the percentage of mycoplasma-positive patients overall may be somewhat lower than found in our studies. This is

reasonable, since the GWI patients that have come to us for assistance may be more advanced patients with more progressed disease than the average GWI patient. We found that patients on antibiotic therapy (n=73) relapsed within weeks after their first 6-week cycle of therapy, but 58/73 recovered after up to six cycles of therapy and 14/73 are still undergoing therapy.¹² GWI patients who recovered from their illness after several (3-7) six-week cycles of antibiotic therapy were retested for mycoplasmal infections and were found to have reverted to a mycoplasma-negative phenotype.¹¹⁻¹² We suggest that the therapy takes a long time because the mycoplasma is slow-growing and is localized deep inside cells in tissues where it is more difficult to achieve adequate antibiotic therapeutic concentrations. As stated above, multiple cycles of therapy resulted in eventual recovery in a high percentage of mycoplasma-positive GWI patients. Only the types of antibiotics that are known to be useful against mycoplasmas were effective; most have no effect at all on the signs and symptoms of GWI/CFS/ME, and some antibiotics make the condition worse. Although anti-inflammatory drugs can alleviate some of the signs and symptoms of GWI, the signs and symptoms quickly return after discontinuing drug use. If this effect was due to an anti-inflammatory action of the antibiotics, then the antibiotics would have to be continuously applied and they would be expected to eliminate only some of the signs and symptoms of GWI. In addition, as mentioned above, not all antibiotics even those with anti-inflammatory effects, work. Thus the antibiotic therapy does not appear to be a placebo effect, because only a few types of antibiotics are effective and some, like penicillin, make the condition worse. Although we have been criticized for not conducting double-blind, controlled clinical studies, such studies are quite labor-intensive and expensive, and all of our studies were conducted without any government support or help whatsoever. We have designed a double-blind, cross-over clinical trial that includes two antibiotics, and we would like to obtain government support for such a trial.

Other Exposures and GWI

We consider it quite likely that many of the Desert Storm veterans suffering from the GWI/CFS/ME/FMS signs and symptoms may have been exposed to chemical/biological cocktails (or endogenous sources of these agents) containing slowly proliferating microorganisms, including pathogenic mycoplasmas and quite possibly other bacteria and viruses. Such infections, although not usually fatal, can produce various chronic signs and symptoms long after exposure. The DoD has maintained that Iraqi offensive Chemical and Biological Weapons were not released during or after the Gulf War, but the appropriate detection equipment to determine whether Biological Weapons were present were not deployed. The Iraqi armed forces were operating under Soviet War Doctrine, which stresses offensive use of combinations of CBW together with conventional weapons. There is evidence that CW were released during and certainly after the conflict when bunkers containing CBW were destroyed. We accept that chemical and/or radiological exposure(s) can result in somewhat similar signs and symptoms, this does not explain the apparent contagious nature of GWI and the delayed appearance of similar GWI/CFS/ME/FMS signs and symptoms in immediate family members.

There were several potential sources of chronic biological agents in the Persian Gulf Theater of Operations.¹⁹ First, deployed soldiers received multiple vaccine inoculations (some experimental) that were given all at once instead of using an appropriate schedule. Simultaneous multiple vaccinations can result in immunosuppression and leave an individual susceptible to opportunistic infections. Some experimental vaccines could also have been contaminated with small amounts of slow-growing microorganisms. Although hotly denied by the DoD, many veterans are testing positive for the presence of a squalene adjuvant (MF59) in their blood, and such adjuvants are only approved for use in experimental vaccines, suggesting that deployed (and some nondeployed personnel who were vaccinated and now have GWI) received experimental vaccines. Some of these experimental vaccines could have been contaminated with small amounts of slow-growing microorganisms. Alternatively, one of the experimental vaccines could have been similar to the HIV-1 vaccine that uses a mycoplasma containing the HIV-1 *env* gene. This is probably the *Mycoplasma fermentans* incognitus strain containing the *env* gene that was found in veterans' blood leukocytes by us. Iraq was known to have extensive stockpiles of BW and the potential to deliver these weapons offensively, at short range in modified biological sprayers that deliver BW onto the sand to create exclusionary zones or 'biological minefields' and at long range in modified SCUD-B (SS-1) missiles with 'skyburst' warheads. As mentioned above, many of the storage and factory facilities where CBW were stored were destroyed immediately up to, during and after the Desert Storm ground offensive, releasing plumes containing these agents high in the atmosphere where

they could be carried downwind ('blow-back' exposures) to our lines. Such possible mechanisms of potential exposure must be carefully examined, not categorically dismissed by DoD personnel in Washington with little first-hand knowledge of the conditions on the ground. There are a number of possible reasons why the DoD and DVA deny that our forces were exposed to Chemical and Biological agents during the Gulf War, and these were discussed by us in a previous article in this journal.¹⁹

The Need for Further Studies

Finally, can GWI be completely explained by chronic bacterial and/or other infections? The answer to this is no. GWI is not one disease; it appears to be a collection of various disorders and illnesses caused mainly by chemical and/or biological exposures that produce complex chronic signs and symptoms. Desert Storm veterans were exposed to a variety of toxic agents in the Persian Gulf, including oil well fires, battlefield smoke, anti-nerve agents, insecticides, or multiple chemical agents, and in some cases radiological agents (depleted Uranium), and many GWI patients now have multiple sensitivities to various chemicals because of these exposures. Chemical exposures can cause toxicological effects and can produce many but not all of the signs and symptoms of GWI.^{20, 21} In addition, chemical exposures can result in immunosuppression and leave an individual susceptible to infections.

Future efforts should be directed at determining the types of exposures that occurred in the Persian Gulf region, including chemical, radiological and biological exposures, and how combinations of these could be involved in causing chronic illnesses. In the case of biological agents or infections where treatments exist, controlled clinical trials will have to be designed and initiated, and the necessary resources to conduct and evaluate these trials will have to be allocated. There is, however, an unexpected benefit from our efforts at understanding the role of chronic infections in GWI. We and other laboratories have now found similar types of chronic infections in a rather large subset of civilian cases of CFS/ME and FMS, and patients with these illnesses have been diagnosed and successfully treated, resulting in recovery of these patients after years of unexplained illnesses. Since there are over one million CFS/ME/FMS patients in the U.S. alone, this means that hundreds of thousands of Americans may be able to regain their health using the diagnostic tests and treatment suggestions developed for GWI.

We believe that the U.S. Congress hold the key to solving the problem of GWI. This and associated disorders (CFS/ME and FMS) must be studied and solutions found using the peer-reviewed grant award system, such as that used by NIH. Efforts to direct funding away from or re-budget allocated funds for CFS and FMS research, such as done over the last several years by NIH, should be stopped. GWI research and treatment cannot be left to the DoD and DVA, because they have not shown themselves to be especially effective or responsive to the health problems of afflicted Gulf War veterans and their family members. We consider it appropriate that civilian scientists and physicians collaborate closely with their counterparts in government to study and solve this problem in as objective manner as possible.

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Drs. Nicolson have been engaged in studying Gulf War Illnesses since their step-daughter returned from service in Desert Storm in 1991 as a Staff Sergeant and Crew Chief of a Blackhawk helicopter in the U.S. Army's 101st Airborne Division (Air Assault) and developed the unusual, multiple signs and symptoms of Gulf War Illness that prevented her from finishing pilot training. Since then the Nicolsos have been involved in a research effort to identify some of the possible causes of and develop treatments for Gulf War Illness patients.

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