What is Gulf War Syndrome (Part I)

by Sue Prophet, RRA, CCS

In 1990 and 1991, nearly 700,000 members of the US armed forces served in the Persian Gulf. Since their return home, thousands of these veterans have reported illnesses they believe are related to their service in the Gulf. Due to the nature of these illnesses, there has been considerable debate over the etiology of the veterans' reported symptoms and whether or not some veterans do indeed have a distinct disease entity related to some type of chemical exposure in the Gulf.

Military experts, veterans' groups, medical experts, and other researchers have all pointed to many risk factors and disease processes as possible causes of the unexplained illnesses in Gulf War veterans. Risk factors include infectious agents (e.g., leishmaniasis), environmental and ambient pollutants (e.g., sand, petroleum and petroleum combustion products, pesticides, chemical agent-resistant coating paint, and smoke from oil well fires), medical prophylaxis (e.g., anthrax and botulinum toxin vaccines and pyridostigmine bromide), depleted uranium munitions, biological and chemical warfare agents, temperature extremes, airborne dust, and physiological and psychological stressors. While some veterans have been diagnosed with specific diseases that are clearly related to their military service -- such as leishmaniasis and malaria -- many others have reported a variety of symptoms that do not clearly point to a specific disease.

Part of the difficulty in ascertaining the etiology of the veterans' physical complaints is the wide assortment of symptoms, encompassing a number of body systems. Reported symptoms include fatigue, joint pain, muscle pain, memory loss, headaches, emotional problems, gastrointestinal complaints, impotence, insomnia, loss of balance, respiratory problems, abnormal weight loss, and sleep disturbances. The severity of these symptoms ranges from mild to completely debilitating. Data from the Department of Defense's Comprehensive Clinical Evaluation Program indicate that the most common primary diagnoses were psychological conditions, multisystemic conditions, and musculoskeletal disorders. Many experts believe the array of symptoms being experienced by many veterans is too broad to fit any single syndrome. Identifying a cause of the veterans' symptoms is also made difficult by the wide array of possible health hazards that veterans were exposed to during the Persian Gulf War.

A number of studies have been and continue to be conducted in an effort to find an answer, or answers, to the reported health problems. Though some scientists believe Iraqi chemical weapons and other poisons released on the battlefield are responsible for many of the reported health problems, other researchers maintain that stress is a more likely cause. To date, there has been no convincing epidemiologic or biological evidence that a single illness or cause explains the variety of symptoms being reported by Gulf War veterans. In fact, results of epidemiologic studies of veterans of the Persian Gulf War showed no overall increase in hospitalization rates, birth defects, or mortality due to medical causes.

War Syndromes

Throughout mankind's history, a correlation between the horrors of war and mysterious illnesses in soldiers and veterans has been observed. Since the US Civil War, two general categories of war-related illnesses have been recognized. One is a poorly understood group thought to be associated with physiologic disease. The other group consists of psychological illnesses attributed to wartime stress. These classifications show that war syndromes have not been consistently defined or identified by a pathognomonic physical sign or laboratory abnormality.

During the US Civil War, soldiers were evaluated for a syndrome called irritable heart. This syndrome was principally characterized by shortness of breath, palpitations, and sharp or burning chest pain, particularly upon exertion. Other symptoms included fatigability, headache, diarrhea, dizziness, and disturbed sleep. There was no consistent sign of physiologic disease, and most patients appeared to be in fair overall health. Because many of these patients had experienced a recent episode of diarrhea, upper respiratory infection, or febrile disease, it was concluded that an infectious disease was the cause in 48 percent of patients. Thirty-five percent of cases were attributed to strenuous military duties and 18 percent to miscellaneous causes. Thirty-eight percent of patients recovered from the disorder. Administration of several drugs, including digitalis, may have had a

beneficial effect, and few patients had conclusive evidence of heart disease. However, symptoms of the irritable heart syndrome also occurred in the civilian population. In addition to irritable heart syndrome, a war-related illness attributed primarily to psychological factors was also reported during this war.

A similar syndrome to irritable heart was also a major problem during World War I. Symptoms included shortness of breath, palpitations, chest pain, fatigue, headache, dizziness, confusion, concentration problems, forgetfulness, and nightmares. This complex of symptoms became known as soldier's heart or the effort syndrome, because symptoms seemed to be exacerbated by effort. It was also called DaCosta syndrome, disordered action of the heart, and was known as neurocirculatory asthenia in the US. At the beginning of World War I, this syndrome was frequently attributed to cardiac hypertrophy caused by heavy marching packs compressing the chest.

As the war progressed, effort syndrome was believed to encompass a mixed group of illnesses and causes, including constitutional nervous and physical weakness; malingering; infectious disease or debility stemming from previous infections; exhaustion from lack of sleep and exertion in the trenches; the effects of poison gas; and, on rare occasion, heart disease. In some cases, the onset of symptoms was also associated with acute stress resulting from combat or burial duties. Although clinical studies published at the end of the war indicated that effort syndrome was caused by psychological factors, there was little agreement on what specific symptoms constituted effort syndrome or whether it was primarily a physiologic or psychological illness. In addition to effort syndrome, an acute illness attributed to combat stress (also called shell shock or trench neurosis) was investigated during World War I. Typical manifestations of acute combat stress reaction included breakdown in battle, dazed or detached manner, exaggerated startle response, and severe anxiety.

Also seen in World War II, the debate over whether effort syndrome was predominantly a physiologic or psychological illness continued. Acute combat stress reaction (also known as battle fatigue, combat exhaustion, or operational fatigue) was a significant problem, and a better understanding of this condition developed during World War II. It was determined that acute combat stress reaction frequently manifested as somatic symptoms, including fatigue, palpitations, diarrhea, headache, impaired concentration, forgetfulness, and disturbed sleep.

During the Korean conflict, acute combat stress reaction was an important clinical problem. Possibly because effort syndrome was attributed to psychological causes during World War II, it was not reported as a major medical problem during the Korean conflict. Since the 1940s, effort syndrome has been identified less frequently as a unique disease entity. However, many illnesses not related to war have been traced back to it, including anxiety neurosis and manic-depressive conditions, panic disorders, mitral valve prolapse syndrome, hyperventilation syndrome, and chronic fatigue syndrome.

Finally, the most prominent illness related to the Vietnam War was post-traumatic stress disorder -- initially called post-Vietnam syndrome. This syndrome is distinct in that acute combat stress reaction is the immediate consequence of psychological trauma, while post-traumatic stress disorder more often refers to the long-term consequences of extreme psychological stress.

Research Studies' Attempts to Explain Gulf War Illnesses

Haley Study

Robert Haley, MD, conducted a study of one military unit that served in the Persian Gulf. His hypothesis was that combinations of cholinesterase-inhibiting chemicals might have caused variants of a general nervous system injury. Many of the veterans with neurologic impairments seemed to have similar symptoms as those of a rare disorder called organophosphate-induced delayed polyneuropathy -- a result of inhibition of the enzyme acetylcholinesterase (a key enzyme of the nervous system function). Some examples of cholinesterase inhibitors are pyridostigmine bromide, the nerve agent Sarin, and organophosphate pesticides.

Haley's research subjects consisted of one military unit, containing 249 soldiers. Of these soldiers, 70 percent reported serious health problems attributed to the war. This study identified clusters of symptoms, which researchers further clustered into syndromes. The researchers believed these syndromes to be variants of organophospate-induced delayed polyneuropathy, brought on by exposure to chemicals that inhibit acetylcholinesterase.

Three primary syndromes were eventually identified: impaired cognition syndrome, confusion-ataxia syndrome, and arthromyoneuropathy syndrome. Impaired cognition syndrome is characterized by distractibility, difficulty in remembering,

depression, insomnia, fatigue, slurring of speech, confused thought processes, and migraine-like headaches. Impaired cognition syndrome appeared to be a milder form of neurotoxicity, resembling the chronic effects of pesticide exposure. Confusion-ataxia syndrome was characterized by problems with thinking and reasoning processes, confusion, disorientation, difficulty balancing, depression, liver disease, sexual impotence, and diagnosis of post-traumatic stress disorder. Generalized joint and muscle pains, increased difficulty lifting heavy objects, fatigue, and tingling or numbness of the hands, arms, feet, and legs characterizes arthromyoneuropathy syndrome.

Haley and his colleagues suggested that wartime exposure to combinations of chemicals such as chemical nerve agents, flea collars, and anti-nerve gas pills among some Gulf War veterans were associated with chronic neurotoxic syndromes. The researchers also suggested that most symptoms of these three syndromes could be explained by varying combinations of injury to the brain, spinal cord, and peripheral nerves. Each of the three primary syndromes was found to be strongly associated with a different set of risk factors reflecting possible exposures to different chemicals.

Veterans with symptoms of these syndromes were found to be four to eight times more likely to have been exposed to pyridostigmine bromide tablets, chemicals in insect repellants, and pet flea collars. They also found that a patient's age was a factor in the variations in symptoms. In the study, impaired cognition syndrome was more common in younger veterans who worked in security or wore pet flea collars to ward off insects. Although the government did not sanction the use of flea collars, some military personnel used them for added protection against desert insects, despite the fact that flea collars contain chlorpyrifos, a neurotoxic chemical that can be absorbed through the skin.

Confusion-ataxia syndrome was more prevalent in veterans who were older, reported exposure to a likely chemical weapons attack, or experienced the side effects of pyridostigmine bromide tablets. Arthromyoneuropathy syndrome was more common in older veterans who used government-issued insect repellant containing 75 percent DEET or experienced side effects from pyridostigmine bromide tablets. Other risk factors, such as exposure to oil well smoke, multiple immunizations, depleted uranium munitions, burning jet fuel, and combat stress were hardly associated at all with the identified syndromes. Veterans who were near an area thought to have been a possible target of chemical weapons attacks were five times more likely to have one of the syndromes than those with only one of the risk factors.

The researchers suggested that different combinations of chemicals interacting with the ages of the exposed veterans could explain the distinct clinical syndromes. Numerous neurologic diseases and injuries are known to cause greater symptomatic disturbances in older people. Haley suggested that some cases of illness may represent neurotoxicity caused by low-dose exposures to chemical warfare agents. He also postulated that the three syndromes might represent variants of a single pathologic process distinguished by severity of impairment or by predominant involvement of different components of the nervous system. Another theory holds that the differences among the syndromes may be due to differences in brain reserve capacity. This reserve capacity possibly interacts with different combinations of cholinesterase-inhibiting chemicals that the veterans were exposed to during the war.

Iowa Study

A study of military personnel from Iowa who served in the Persian Gulf found that military personnel who served in the Persian Gulf War have a higher self-reported prevalence of medical and psychiatric conditions than do military personnel who served elsewhere during the same time period. Of the 3695 subjects who took part in the study, 14.7 percent reported symptoms of two or more medical and psychiatric conditions versus 6.6 percent of soldiers who did not serve in the Persian Gulf. The conditions identified in this study included symptoms of depression, posttraumatic stress disorder, chronic fatigue, cognitive dysfunction, bronchitis, asthma, fibromyalgia, alcohol abuse, anxiety, sexual discomfort, and diminished mental and physical functional health. The conditions reported by Persian Gulf veterans in the Iowa study were found to be more common among those veterans reporting exposures to solvents, smoke, pesticides, pyridostigmine bromide, and chemical warfare agents than among those not reporting such exposures.

The researchers offered several possible explanations for the higher prevalence of symptoms of medical and psychiatric conditions among Persian Gulf War veterans:

- A distinct cause or exposure may be responsible for each of the reported conditions

- One specific psychiatric condition, such as depression, may represent the primary medical condition associated with the Persian Gulf War
- Exposures or prophylactic measures found to be safe and well-tolerated alone may act synergistically with other exposures encountered in military settings -- causing a more severe disease
- Those veterans with symptoms involving several organ systems may have a multisystemic condition that does not fit well into an established disease category
- The conditions reported by Persian Gulf War military personnel may not be unique to the Persian Gulf War. The reported symptoms are analogous to conditions reported by veterans of other wars, dating back to the Civil War, which may indicate they are due to the experience of warfare rather than to a specific exposure

It is important to note that many experts have discounted the Iowa and Haley studies because they are based on relatively small sample sizes and are limited by self-selected, self-reported symptom assessment.

Other Research Hypotheses

Claudia Miller, MD, environmental and occupational medicine specialist, Department of Family Practice at the University of Texas Health Science Center, suggested that the veterans' symptoms are due to a new general disease mechanism. Her theory is that an exposure to toxic chemicals will cause extremely low levels of chemicals to trigger symptoms. Miller suggested that the veterans' illnesses may represent a new class or family of disorders.

Howard Kipen, MD, chief of the occupational division, Robert Wood Johnson Medical School in Piscataway, NJ, believes the mysterious illnesses are a factor of a combination of chemical and pesticide exposures with psychological stress.

Governmental Conclusions

Department of Defense

The Department of Defense maintains that Gulf War veterans suffered no greater rate of mortality or morbidity than would be seen in any other group of 700,000 Americans of similar ages. A Department of Defense study of more than 1000 sick veterans indicated that 60 percent had physical ailments with known causes -- findings that were not disproportionate to their occurrence in the general population. Another 25 percent had psychological disturbances, including depression and post-traumatic stress disorder. About 15 percent had unexplained ailments, including headache, memory loss, fatigue, sleep problems, and intestinal and respiratory symptoms. The majority of cases in the Persian Gulf health registries were diagnosed with specific illnesses, 20 percent remain undiagnosed, and about 10 percent had no detectable symptoms.

The Department of Defense emphasizes stress as the principal cause of the veterans' symptoms. It maintains that low-level chemical exposures do not result in delayed or chronic health effects in the absence of acute symptoms at the time of the exposure.

For several years, the US government denied that its troops were exposed to chemical weapons in the Persian Gulf. But in June 1996, the Pentagon acknowledged the likelihood that some military personnel were exposed to chemical warfare agents from fallout following detonation of Iraqi munitions bunkers in Kamisiyah.

Department of Veterans' Affairs

The Department of Veterans' Affairs' (VA's) position, like that of the Department of Defense, is that low-level asymptomatic chemical exposures have not been shown to cause delayed or long-term health effects. However, the VA recognizes the scarcity of scientific literature on this issue and the fact that further research is needed.

The VA has not found evidence in the Persian Gulf Health Registry to support a hypothesis that exposures to nerve agents are responsible for the illnesses of the majority of ill Persian Gulf veterans. In keeping with these findings, the VA consistently

diagnosed veterans with the unexplained symptoms as stress-related, such as post-traumatic stress disorder or other psychological conditions.

Centers for Disease Control and Prevention

The Centers for Disease Control and Prevention (CDC) conducted a study of a specific military unit of 59 Gulf War veterans. This study found that the prevalence of 13 chronic symptoms was significantly greater among those deployed to the Gulf than among those who were not. The Gulf War veterans studied showed a significant and progressive decline in functioning and well being. These findings were not associated with physical examination or laboratory abnormalities. The illnesses were not associated with any known infectious agents. There were notable similarities between the undiagnosed problems and two known conditions -- chronic fatigue syndrome and posttraumatic stress disorder.

The CDC developed a working case definition of Gulf War illnesses. It defined a case as "at least one chronic (present for six months or longer) symptom from two or more of the following categories: fatigue; mood and cognition-related symptoms (feeling depressed, difficulty remembering or concentrating, feeling moody, feeling anxious, trouble finding words or lack of interest in sex); and musculoskeletal-related symptoms (joint pain, joint stiffness)."

Central Intelligence Agency

The Central Intelligence Agency's (CIA's) Office of Weapons, Technology, and Proliferation conducted an independent review of intelligence documents to determine whether troops were exposed to chemical and biological warfare agents during the Gulf War. Its review concluded that Iraq did not use chemical or biological weapons or deploy these weapons in Kuwait. The CIA assessed that Coalition forces destroyed no biological weapons or agents during the Gulf War. Its conclusion, in line with that of the Department of Defense, is that a nerve agent was released as a result of postwar demolition of an Iraqi munitions bunker. The CIA found no evidence indicating that Iraq developed agents specifically intended to cause the most common types of long-term symptoms seen in ill Gulf War veterans.

House Committee on Government Reform and Oversight

After a 20-month congressional investigation of Gulf War illnesses, the House Committee on Government Reform and Oversight concluded that a variety of toxic agents in the Gulf War, including Iraqi chemical weapons and pesticides, were probably responsible for the health problems reported by many veterans.

The House report acknowledged that the mystery surrounding the illnesses reported by Gulf War veterans may remain a mystery for years. Specifically, the House Committee's report of its investigation included the following findings:

- The presence of a variety of toxic agents during the Gulf War strongly suggests exposure plays a role in causing, triggering, or amplifying subsequent service-connected illnesses
- Gulf War veterans were not trained to protect themselves from the effects of exposure to depleted uranium dust and particles
- Pyridostigmine bromide can have serious side effects and interactions when taken in combination with other drugs, vaccines, chemical exposures, heat and/or physical exercise
- VA and Department of Defense health registry diagnostic protocols relied on the unfounded conclusion that there were no chemical, biological, or other toxic exposures to US troops in the Gulf War
- VA and Department of Defense health registry diagnostic protocols have been based on the unwarranted conclusion that, unless there is an immediate and acute reaction, exposure to chemical weapons and other toxins do not cause delayed or chronic symptoms
- VA and Department of Defense physicians relied on diagnoses of somatoform disorder and post-traumatic stress disorder to explain Gulf War veterans' illnesses

- There is no credible evidence that stress or post-traumatic stress disorder causes the illnesses reported by many Gulf War veterans
- Accurate diagnosis of veterans' illnesses remains difficult due to inadequate or missing personal medical records, missing toxic detection logs, and unreleased classified documents
- Exposures to low levels of chemical warfare agents and other toxins can cause delayed, chronic health effects

This article is the first in a two-part series. See Coding Notes in September for a look at the Presidential Advisory Committee's findings on Gulf War Syndrome.

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Article citation:
Prophet, Sue. "What is Gulf War Syndrome? (Part I)." *Journal of AHIMA* 69, no.7 (1998): 70-76.
