What is Gulf War Syndrome (Part II)

by Sue Prophet, RRA, CCS

Presidential Advisory Committee on Gulf War Veterans' Illnesses

President Clinton established the Presidential Advisory Committee on Gulf War Veterans' Illnesses in May 1995 to ensure an independent, open, and comprehensive examination of health concerns related to Gulf War service. This committee examined exposure and expected health effects for 10 Gulf War risk factors: pesticides, chemical weapons, biological weapons, vaccines, pyridostigmine bromide, infectious disease, depleted uranium, oil-well fire smoke, petroleum products, and psychological and physiological stress. The committee determined that most of these risk factors are unlikely to be associated with the health problems currently reported by Gulf War veterans. The committee concluded that although some veterans clearly have service-connected illnesses, current scientific evidence does not support a causal link between the symptoms and illnesses reported by veterans and exposures to these risk factors. The panel suggested that further investigation is needed in areas of uncertainty, such as the long-term effects of low-level exposure to chemical warfare agents and the synergistic effects of exposure to pyridostigmine bromide and other risk factors.

Specifically, the Presidential Advisory Committee's report of its investigation included the following findings:

- Gulf War veterans have experienced no excess mortality from natural causes during or after the war. Gulf War veterans have experienced excess mortality from external causes, such as injuries, which is consistent with the experience of veteran populations from previous conflicts
- Information from the clinical programs indicates that musculoskeletal and ill-defined conditions are common components of Gulf War veterans' illnesses
- Data from clinical programs and epidemiological studies indicate stress-related disorders are common components of Gulf War veterans' illnesses
- Among the subset of the Gulf War veteran population examined in the ongoing clinical and research programs, many veterans have illnesses likely to be connected to their service in the Gulf. Currently, the extent of service-connected illness in the population is unknown
- Stigmatization of psychosomatic illness seriously interferes with some veterans seeking care
- It is unlikely that exposures in the Gulf War theater are responsible for the birth defects of children born to veterans

The presidential panel recommended that:

- Research on possible causes and methods of prevention of excess mortality from external causes among veterans should receive high priority
- Research on Gulf War veterans' illnesses should emphasize investigating the causes and methods of prevention and treatment of musculoskeletal conditions
- Research on Gulf War veterans' illnesses should emphasize investigating the causes and the methods of prevention and treatment of stress-related disorders

- Since the stigmatization of mental illness continues to be a problem for society at large, the Department of Health and Human Services should place a priority on developing public education outreach programs that note the indissoluble association between the mind and the body

- A permanent program should be created in which the Department of Veterans' Affairs would contract with the National Academy of Sciences to conduct a research review. The Academy would be charged with examining available scientific evidence to study possible associations between illness and service in the Gulf War. This analysis would make determinations regarding statistical associations between Gulf War service and morbidity and mortality and whether a plausible biological mechanism exists

Based on the advisory panel's report, the president proposed an increase in research funds to investigate the effects of low-level exposure to chemical agents and other possible causes of the mysterious illnesses. The president also called for the creation of a medical records system, known as the Force Health Protection Program, that would track military personnel injuries, illnesses, inoculations, and exposure to potential hazards.

Risk Factors Examined by the Presidential Advisory Committee as Potential Causes of Gulf War Illnesses

Pesticides

There were five categories of pesticides the Department of Defense shipped for use during the Gulf War: organophosphorus (OP) pesticides, methyl carbamate pesticides, organochlorine pesticides, pyrethroid pesticides, and DEET.

When administered in high doses, OP pesticides cause irreversible inhibition of acetylcholinesterase, an enzyme crucial to normal nerve and nerve/muscle function. Exposure to organophosphates can produce an acute, immediate reaction that may result in death. This reaction is due to the paralysis or binding of an enzyme called cholinesterase, which causes labored breathing, diarrhea, and ultimately, death due to terminated breathing.

Some experts believe that a lesser exposure to organophosphates can cause a delayed reaction several weeks or months later. This delayed reaction can result in spectra of neurological dysfunctions, which can be permanent. Peripheral neuropathy could develop. The spinal cord might be involved, resulting in the development of spasticity. These experts believe that when the exposure is periodic and over a long period of time, or at a low level, the individual might experience less severe symptoms, such as dizziness or difficulty concentrating.

Immediate symptoms of OP pesticide poisoning in humans usually develop within four hours of exposure and include narrowing of the eye's pupil (miosis), headache, nausea, dizziness, anxiety, and restlessness. Severe and rapid onset poisoning symptoms include muscle twitching, weakness, tremor, incoordination, vomiting, abdominal cramps, diarrhea, sweating, salivation, tearing, runny nose, and production of phlegm. Life-threatening symptoms include unconsciousness, incontinence, convulsions, and depression of breathing function. According to the Department of Defense, its medical monitoring and surveillance efforts reported no cases of immediate and severe OP poisoning symptoms in US military personnel during the Gulf War.

Some individuals who recover from immediate and severe OP poisoning show long-term (lasting more than one year), subtle, neuropsychological abnormalities. Clear but subtle differences in intellectual functioning, academic skills, abstraction and flexibility of thinking, and simple motor skills have been noted.

Some OP pesticides that are no longer sold in the US have been associated with human cases of a second type of delayed toxic effect called organophosphate-induced delayed neurotoxicity (OPIDN, sometimes referred to as delayed neuropathy). Initial symptoms are muscular incoordination progressing to numbness, tingling, fatigue or a cramp-like pain in the calf muscles, and even moderate to severe muscular weakness and paralysis. Typically, these effects occur seven to 14 days following recovery from immediate and severe poisoning by the OP pesticide and involve neuropathologic lesions and degeneration of the nerve axon and myelin nerve sheath in both the central and peripheral nervous systems.

The pyrethroid insecticide permethrin was used in the Gulf War as an insect repellent. Permethrin is used widely in the US as the active ingredient in personal care products, such as shampoos and lotions, and for treating clothes to make them insect repellent. There are few reported poisonings of humans by permethrin, most likely because such a large dose is required to

cause poisoning. Humans rapidly detoxify and excrete permethrin. Clinical signs of immediate permethrin poisoning following large oral doses become evident within two hours and include incoordination, ataxia, hyperactivity, and convulsions, followed by prostration, paralysis, and death. The presidential panel found no reports of long-term effects from permethrin poisoning in humans.

An organochlorine pesticide, lindane, was used in the Gulf region. Lindane, which was once widely used in the US as an agricultural insecticide, is available as a lotion to treat head and body lice and scabies. Lindane is dermally absorbed, stored in body fat, and only slowly leaves the body. There have been documented reports of a few cases of blood disorders and seizures when large amounts of lindane were used. Under conditions of extremely high exposure, lindane can cause liver and kidney disease.

DEET has been widely used as a liquid insect repellent. Relative to most pesticides, DEET has notably low immediate toxicity. Although generally well tolerated when used as an insect repellent applied to human skin, about 5 to 9 percent is absorbed through the skin, and there have been reports of tingling, mild irritation, and occasional skin peeling following repeated application. In the past 35 years, there have been a few reports of rare neurotoxic effects. Ingestion of enormous amounts of DEET has been associated with immediate toxic effects, including tremors, generalized seizures, and coma, although no long-term effects of poisoning have been reported.

According to the Department of Defense, there were no reports during the Gulf War of symptoms indicating pesticide poisoning. Since evidence from studies of humans poisoned by OP pesticides suggests that low-level exposures that do not cause signs and symptoms of immediate and severe poisoning will not result in long-term health effects, the presidential panel concluded that it is unlikely that health effects and symptoms reported today by Gulf War veterans are the result of exposure to pesticides during the Gulf War. [1]

Chemical Warfare Agents

Since the US believed Iraq had chemical weapons, US forces were supplied with protective gear, detectors, and prophylactic drugs to protect against the known consequences of exposure.

Nerve agents are designed to incapacitate and kill humans. Inhalation exposure to these agents leads to immediate effects, including miosis, runny nose, and increased salivation. Immediate effects following skin exposure include local sweating and muscle twitching. Eye exposure rapidly produces miosis, which often is associated with eye pain, headache, and blurred vision. Higher doses of these agents cause more severe effects, including convulsions, neuromuscular blockage, profuse airway obstruction, and apnea developing within one to two minutes of exposure. Death occurs due to respiratory paralysis. The effects of nerve agent poisoning are virtually identical to those of severe OP pesticide poisoning. Because nerve agents are chemically similar to OP pesticides and affect the same enzyme system in the body, similar long-term health effects would likely occur in the aftermath of immediate, severe poisoning. Scientific evidence suggests that subclinical exposure to nerve agents does not result in long term neurophysiological and neuropsychological health effects.

With mustard agents, poisoning symptoms are severe irritation and tissue damage to eyes, skin, and respiratory and gastrointestinal tracts. Usually the onset of symptoms is delayed for some hours after exposure. The Institute of Medicine has concluded that several specific chronic diseases are causally associated with mustard agent exposure. These include various respiratory cancers, skin cancer, chronic skin ulceration and scar formation, chronic respiratory diseases including asthma, chronic bronchitis, emphysema, chronic eye diseases, and various psychological disorders, including posttraumatic stress disorder.

Based on available data, the presidential panel concluded that it is unlikely the health effects reported by Gulf War veterans today are the result of exposure to chemical warfare agents. Scientific literature indicates that when exposure to chemical weapons results in immediate and severe poisoning, long-term, subtle neuropsychological and neurophysiological effects could occur. Scientific evidence does not indicate that such long-term effects occur in humans following low-level exposures, but the amount of data from either human or animal research on low-level exposures is minimal.

Biological Warfare Agents

It was also believed that Iraq might use biological weapons, particularly anthrax, botulinum toxin, and aflatoxin.

Anthrax is a bacterial disease most often found in cattle and sheep. Human infection can occur by contact with infected animals or by inhalation of spores from infected animal products. Left untreated, the disease is usually fatal. After exposure, the anthrax bacteria travel to the intestines and other areas where they cause severe tissue damage. Initial symptoms include nonspecific malaise, low-grade fever, and nonproductive cough. As the disease progresses, symptoms include high fever, labored breathing, choking cough, and vomiting. Death usually occurs within four days. Terminal symptoms include abrupt onset of shortness of breath, harsh breathing, skin turning blue, excessively rapid heartbeat, and rapid progression to shock and death. No long-term effects have been reported in individuals successfully treated for anthrax.

Botulinum toxin is a group of related, highly poisonous protein agents isolated from fermentation of the bacterium Clostridium botulinum, which occurs naturally in soil and can grow in many meats and vegetables. Botulinum toxin is fast acting, usually producing symptoms within 18 to 36 hours after ingestion. Death occurs in 80 percent of an exposed population after one to three days. Botulinum toxin blocks neuromuscular conduction by binding to receptor sites on motor nerve terminals and by inhibiting the release of acetylcholine. Symptoms at high exposure levels can include respiratory distress and respiratory paralysis, which may persist for six to eight months. Disability progresses from difficulty in walking and swallowing and impaired vision and speech to convulsions. Ultimately, symptoms include paralysis of the respiratory muscles, suffocation, and death, all within a few hours or days, depending on the amount of toxin ingested. Botulism antitoxin can be effective if administered within days of exposure. Scientific literature does not indicate adverse long-term health effects from low-level exposure to botulinum toxin. In fact, it has conventional medical therapeutic uses. Botox is an FDA-approved botulinum toxin, which is injected into the muscle and causes a localized, temporary denervation and muscle paralysis. It is useful in treating a number of conditions, such as blepharospasm, and for use in certain types of eye surgery.

Aflatoxin is a naturally occurring toxic metabolite from certain fungi that sometimes occurs on grains, peanuts, and other foods stored under certain conditions. Aflatoxin ingestion can result in immediate, toxic effects in many different species, and death results from acute liver toxicity. Symptoms of aflatoxicosis include vomiting, abdominal pain, pulmonary edema, gastrointestinal hemorrhage, convulsions, coma, and death. The only documented health effect that could be expected from low-level exposure to aflatoxin would be an increased prevalence of liver cancer, years to decades after exposure.

As stated before, no known long-term health consequences exist in cases where an individual survives exposure to anthrax or botulinum toxin. And the only known long-term effect of aflatoxin exposure is an increased risk of liver cancer. In any case, the available evidence does not support exposure to any of these agents during the Gulf War. Therefore, the presidential panel concluded that it is unlikely the Gulf War veterans' current health problems are the result of exposure to biological weapons.

Anthrax and Botulinum Toxoid Vaccines

In addition to a number of other vaccines, some US military personnel deployed to the Persian Gulf were given vaccines for protection against anthrax and botulinum toxin. Anthrax vaccine is FDA-approved, but botulinum toxin vaccine is considered investigational by the FDA.

Historical data for short-term health effects of the anthrax vaccine indicate that up to 6 percent of recipients experience mild discomfort, including tenderness, redness, swelling, or itching at the inoculation site for up to 72 hours. Less than one percent experience a more severe local reaction that potentially limits the use of the arm for one to two days. Systemic reactions are uncommon. Data regarding botulinum toxin vaccine also indicate that local effects (similar to those experienced with other types of vaccinations) may occur, but systemic reactions are less common. The presidential panel concluded it is unlikely that health effects reported by Gulf War veterans are the result of these vaccines, either alone or in combination.

The presidential committee examined a hypothesis that some illnesses could be the result of contamination of anthrax vaccine by Mycoplasma incognitus. However, they concluded this was unlikely because Mycoplasma cannot survive in either the anthrax or botulinum toxin vaccines.

Pyridostigmine Bromide

Pyridostigmine bromide is a pretreatment drug used to protect against chemical weapons. This drug is approved by the FDA for use in the treatment of myasthenia gravis. No long-term effects have been reported by patients with this disease who have taken pyridostigmine bromide over many years or decades. Reported side effects of this drug include increased salivation,

increased tearing, urinary urgency and frequency, nausea, vomiting, muscle weakness, abdominal cramps and diarrhea. These effects disappear when individuals stop taking the drug.

Some researchers have hypothesized that pyridostigmine bromide, in combination with other risk factors such as stress, the insect repellent DEET, and the insecticide permethrin, may create central nervous system effects. One hypothesis is that the onset of stress makes the blood/brain barrier susceptible to pyridostigmine bromide leakage, increasing its ability to cause damage to the central nervous system. Some researchers have also suggested that the immediate toxicity of the OP pesticides could have been increased from co-exposure to pyridostigmine bromide. However, there were no immediate and severe effects of OP pesticide poisoning reported during the Gulf War, and scientific evidence does not indicate that long-term health effects occur in the absence of immediate poisoning.

The presidential panel concluded it is unlikely that health effects reported by Gulf War veterans are the result of exposure to pyridostigmine bromide. However, the panel did recommend that further research be conducted concerning the synergistic effects of this drug and other risk factors.

Endemic Infectious Diseases

Viscerotropic leishmaniasis and cutaneous leishmaniasis are the only endemic infectious diseases demonstrated to cause chronic morbidity among a number of Gulf War military personnel. These diseases are transmitted through the bites of sand flies. Person-to-person infection does not occur. Cutaneous leishmaniasis causes a characteristic ulcerative or nodular skin rash that can persist for more than a year without treatment. Viscerotropic leishmaniasis can be difficult to confirm, but it was not a cause of widespread illness in Gulf War veterans. Individuals with the unexplained Gulf War illnesses lack signs and symptoms characteristic of these diseases.

The presidential panel concluded it is unlikely that infectious diseases endemic to the Gulf region are responsible for long-term health effects in veterans, except in a small, known number of individuals.

Depleted Uranium

Since depleted uranium is twice as dense as lead, it was used to improve the performance of both armor and armor-penetrating munitions during the Gulf War. The kidney is the organ most sensitive to exposure to uranium. However, there is little epidemiologic evidence of excess kidney disease among mine workers who have been exposed to uranium for years or decades.

The presidential panel concluded it is unlikely that health effects reported by Gulf War veterans are the result of exposure to depleted uranium.

Oil Well Fire Smoke

At the end of the Gulf War, numerous Kuwaiti oil wells and several pools of spilled oil were left burning after being ignited by retreating Iraqi troops. Huge plumes of billowing smoke from these fires rose high into the atmosphere. Occasionally, the smoke remained near the ground, enveloping some US military personnel.

Known immediate health effects from inhaling large amounts of smoke and particulates are primarily respiratory, including coughing, wheezing, increased airway resistance, and respiratory infections. Toxic gases that can be found in oil well fire smoke (such as hydrogen sulfide and sulfur dioxide) can cause eye and nose irritation, decreased pulmonary function, and increased airway reactivity. Nevertheless, these toxic gases were not detected at higher levels during the fires. High levels of airborne particulates, which sometimes occurred in the Gulf region, are associated with increased rates of asthma and can exacerbate other chronic respiratory conditions. With chronic (months or years) exposure to particulates, there is increased risk of some loss in lung function or chronic bronchitis, especially in cigarette smokers.

Oil well fire smoke appears not to have caused observable changes in lung tissue.

Some chemicals contained in oil well fire smoke are human carcinogens. However, the amounts of these pollutants in the air were low. The US Army concluded that the potential for significant long-term adverse health effects for exposed personnel was minimal.

The presidential panel concluded it is unlikely exposure to oil well fire smoke is responsible for symptoms currently reported by Gulf War veterans.

Petroleum Products

Diesel, kerosene, gasoline, jet fuel, and other petroleum-based fuels were widely used during the Gulf War for dust suppression, waste incineration, and for fueling vehicles, stoves, heaters, and generators.

When burned, petroleum fuels produce a variety of potentially hazardous combustion products. High-level, short-term exposures to fuel solvents can cause immediate effects. In most cases, complete recovery occurs when the exposure ceases.

US service members could have been exposed to petroleum fuels by inhalation, ingesting contaminated water or dust, and skin contact. Inhalation exposure could depress the central nervous system. Symptoms include short-term effects ranging from fatigue, headache, nausea, blurred vision, and dizziness, to convulsions, paralysis, and loss of consciousness, depending on the dose. Prolonged breathing of diesel fuel vapors can damage kidneys or lower blood clotting ability. Exposure to high, nonlethal levels is usually followed by complete recovery, although rare cases of permanent brain damage after massive exposure have been reported in the scientific literature.

The presidential panel concluded that, although certain subsets of Gulf War military personnel could have experienced occupational exposures to petroleum products that would entail increased risks of health problems, it is unlikely that health effects reported today by Gulf War veterans are due to exposure to petroleum products.

Psychological and Physiological Stress

Virtually all Gulf War military personnel were exposed to a wide range of stressors associated with the war. These stressors included the bleak, physically demanding desert environment and crowded housing conditions with little personal privacy and few amenities. It was not known that coalition forces would win a quick war with relatively few battle casualties. Also, there was the constant fear that Iraq might use devastating chemical and biological weapons.

Scientists have begun to unravel the physiological connection between the brain and other parts of the human body. Studies have demonstrated that stress can have measurable effects on the brain, immune system, cardiovascular system, and various hormonal responses. Although the human body can adapt to normal stresses, if the stress lasts a long time it can be expressed in a variety of symptoms of physical illness. Today, physicians recognize that many physical and psychological diagnoses are the consequences of stress. It is also known that substantial variability in individuals' responses to stress occurs. Significant evidence supports the likelihood of a physiological, stress-related origin for a number of ailments.

The presidential panel noted that stress does not cause a unique illness or set of symptoms, rather, it can contribute to a broad range of physiological and psychological illnesses. Since stress manifests itself in diverse ways, the panel concluded it is likely to be an important contributing factor to the broad range of physiological and psychological illnesses reported by Gulf War veterans.

Low-Dose Exposure Theory

There are differences of opinion among the experts regarding whether or not low-dose exposure to pesticides or other chemicals can produce chronic effects.

The US Department of Defense has acknowledged that neurotoxic chemical warfare agents had been released in certain areas in the Persian Gulf during the destruction of Iraqi ammunition bunkers after the war. Acute high-dose exposure to chemical warfare agents can cause devastating damage to the nervous system. However, it is not yet clear whether low-dose exposure to chemical warfare agents can cause chronic neurotoxicity. The Department of Defense has taken the position that current medicine acknowledges the fact that chronic symptoms or physical manifestations do not later develop among individuals exposed to low levels of chemical agents who did not first exhibit acute symptoms of toxicity. However, not all of the experts agree. Some experts have stated that pyridostigmine bromide may have masked any acute effects of chemical exposure. It is possible that multiple, low-level chemical exposures could result in a synergistic effect. The symptoms of low-level exposure might not appear for several years after the exposure.

Further study is needed regarding the possible development of chronic health effects after exposure to chemical agents that did not immediately result in any acute effects.

Conclusion

No "silver bullet" has been found to explain or cure Gulf War Syndrome. Gulf War Syndrome is not a discrete syndrome at all, but a variable cluster of symptoms and disease states with different triggers and susceptibilities. Many experts believe that the variety of symptoms reported by veterans makes it unlikely that a single etiologic cause is responsible for producing Gulf War illnesses.

Many physicians and scientists believe that exposure to a wide range of chemicals can produce synergistic effects and cause a variety of health problems. Some experts subscribe to this theory as an explanation for the illnesses. Other experts believe the different illnesses are due to the differing exposures military personnel may have encountered. Due to the principle of biological variation, different cells and different individuals experience different degrees of acute and chronic effects. The differences in type of illness, severity of illness, and the subsequent development of any illness may depend on a number of factors, such as the individual's state of health, duration of exposure or intervals between exposures, and "detoxification capacity" (e.g., genetic susceptibility to a particular type of exposure).

The precise causes of illness in most Gulf War veterans may never be known with certainty. There are a number of challenges to identifying a cause or causes. Classifying the symptoms and identifying illnesses of Gulf veterans is difficult. From the outset, symptoms reported by veterans have been varied and difficult to classify into one or more distinct illnesses. It has thus been difficult to develop a case definition (i.e., a reliable way to identify individuals with a specific disease), which is a criterion for doing effective epidemiological research. Most epidemiological studies on Gulf illnesses have relied only on self-reports for measuring most of the agents to which veterans may have been exposed. Information gathered from Gulf veterans gathered years after the war may be inaccurate or biased. There is often no straightforward way to test validity of self-reported exposure information. As a result, findings from these studies may be spurious or equivocal. Gulf veterans were typically exposed to a wide array of chemical agents, making it difficult to isolate and characterize the effects of individual agents or to study their combined effects. There is no pathognomonic set of signs or symptoms; nor is there a diagnostic test or biomarker for chronic toxicity to neurotoxic chemical agents. Causal inference in most cases is not scientifically possible, unless exposure has been quantified by specific measurement and accurately documented. The question, "Who was exposed to what and in what amount were they exposed?" may never be known due to missing or lost records. Personal medical records of veterans, including sick call records, are inadequate or missing. Most of the military nuclear-biological-chemical (NBC) logs, which are records of toxic warfare agent detections, are missing or destroyed. Readouts from chemical detection equipment have vanished. Many CIA intelligence logs concerning Iraqi chemical and biological weapons storage depots and manufacturing facilities, and documents concerning enemy capabilities and intentions to use chemical or biological weapons against US troops have remained classified since the Gulf War. Without valid and reliable data on exposures and the multiplicity of chemical agents to which the veterans were exposed, researchers will likely continue to find it difficult to detect relatively subtle effects and to eliminate alternative explanations for Gulf War veterans' illnesses.

Code Assignment

There is no specific ICD-9-CM code for Gulf War Syndrome. As this article has pointed out, the etiology of Gulf War Syndrome, or even whether or not it is a distinct disease entity, remains unknown. When the physician has documented a diagnosis of Gulf War Syndrome or Illness, assign codes for the documented manifestations (per *Coding Clinic for ICD-9-CM,* First Quarter 1998). Assign code E999, Late effects of injury due to war operations, as an additional code.

Note

1. Some researchers believe that pesticide exposure might have been harmful when combined with other chemical risk factors.

References

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This article is part two in a two-part series. See "Coding Notes" in July/August for the history of war syndrome, and research on Gulf War Syndrome.

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