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Gulf War Illnesses
Testimony to the Senate Veterans Affairs Committee

September 25, 2007

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Thank you very much for your invitation to discuss Gulf War Illnesses and ideas for improved research and treatment of affected veterans. I practice general internal medicine, have a background in bioterrorism, anthrax and vaccine injuries, and have conducted a clinic for Gulf War (GW) veterans and others with multi-symptom syndromes (fibromyalgia, chronic fatigue syndrome, multiple chemical sensitivity) since 1999.

Because so much confusion and controversy has surrounded this illness, I thought it would be helpful to discuss persisting issues using a question and answer format, while reviewing recent literature on Gulf War Illnesses. I hope to clarify what is already known, as well as what needs to be known in order to provide the best treatment to affected veterans. I will then discuss my treatment approaches. I use the terms Gulf War Illnesses (GWI) and Gulf War Syndrome (GWS) interchangeably.

1. What is Gulf War Syndrome?

As early as 1993, Senator Donald Riegle's staff produced a report that said, "Over 4,000 veterans of the Gulf War suffering from a myriad of illnesses collectively labeled "Gulf War Syndrome" are reporting symptoms of muscle and joint pain, memory loss, intestinal and heart problems, fatigue, running noses, urinary urgency, diarrhea, twitching, rashes and sores." In 1998 CDC developed a case definition of the illness, which omits some common symptoms, but confirms the illness Riegle's staff identified, and provides clinicians with a reasonable basis for diagnosing veterans and starting treatment. So there is a long, well-documented history of the reality of this illness.

Yet many physicians are unaware of the CDC case definition, and have been bamboozled by the media into thinking Gulf War Illnesses either do not exist, are psychosomatic or a result of stress. Surprisingly, this includes physicians at VA facilities who care for affected patients. This widespread ignorance is compounded by the VA treatment guidelines (posted on the VA website for clinicians), which emphasize the use of psychotropic medications and cognitive behavioral

therapy, although the science to support this is exceedingly weak.

An estimated 200,000 1991 Gulf War veterans (25-30% of all deployed veterans) and some vaccinated, nondeployed Gulf "era" veterans suffer from illnesses related to their service, and have been awarded partial or full disability benefits by the VA. Although the signs, symptoms and severity of illness vary considerably between affected veterans, the combination of symptoms known as "Gulf War Syndrome" probably affects most of the 200,000 veterans who are ill.

Their symptoms are not confined to the CDC's defining triad of musculoskeletal pain, fatigue and cognitive and/or emotional disturbance. Their medical conditions have been variously described in different studies. For example, one UK study found that Gulf War veterans were 20 times as likely as other veterans to complain of mood swings, 20 times as likely to complain of memory loss and/or lack of concentration, and 5 times as likely to complain of sexual dysfunction. It is my opinion that the increased mental disorders reported in GW veterans reflect central nervous system (brain) dysfunction, manifested in a variety of ways.

Furthermore, some affected veterans have developed anxiety and/or depression as a result of their loss of function, as well as frustration resulting from the lack of validation of their illnesses by DOD, VA and civilian health providers, and failure to receive beneficial treatment. Many veterans have endured the suspicion of military superiors and colleagues, friends and family that they are malingering, a result of the mediocre level of much popular and professional discourse about this illness.

2. Can we make medical sense of the multiple symptoms that occur in Gulf War veterans?

According to Gronseth, "Although an objective marker to GWS would be useful for studies, the absence of such a marker does not make the syndrome any less legitimate... The real debate surrounding medically unexplained conditions is not whether or not they exist, but defining their cause."

Many patients with GWS meet criteria for other medically unexplained conditions, also known as multi-symptom syndromes, such as chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivity. These conditions are poorly understood, but have a very similar pattern of symptoms and findings as GWS. Some underlying mechanisms have been shown to be the same as well.

An important VA study in which 1000 deployed 1991 Gulf War and 1000 nondeployed Gulf era veterans were carefully examined 10 years after the Gulf War, found that deployed veterans were 2.3 times as likely to have fibromyalgia, and 40.6 times as likely to have chronic fatigue syndrome as nondeployed era veterans, confirming a relationship between these conditions and GWS.

3. Does the CDC case definition identify all deployment-related illnesses in Gulf War veterans?

No. We know ALS (amyotrophic lateral sclerosis or Lou Gehrig's disease) occurs twice as often in GW vets as in the civilian population, but it also occurs 50% more often in soldiers in general. The military exposures leading to these increased ALS rates are unknown.

Possible reasons ALS has been studied more carefully in GW veterans than other illnesses, are that a) veterans develop the illness at a younger age than the civilian population, b) Congressional testimony by affected, now deceased Gulf War veteran Michael Donnelly in 1997 gave the illness visibility, and c) ALS only affects a small number of people.

Chronic diarrhea is another illness commonly seen in GW veterans, but it is not included in the CDC's case definition. GW veterans have developed a variety of other medical illnesses. What we still don't know is whether there are, for instance, more heart attacks in deployed GW veterans than there would have been, had they not deployed. The research is contradictory on whether various illnesses occur more often in Gulf War veterans, although several studies list a large number of symptoms that are seen more commonly in GW veterans.

4. Why don't we know whether deployed veterans have more illnesses (like heart attacks) than they would have otherwise?

The results of research depend on the methods used to investigate the research question. Epidemiological research is limited to evaluating a statistical relationship between an exposure and an illness. But statistically significant relationships occur for many reasons other than cause and effect. Thus, statistics alone cannot prove cause and effect. Only when all other factors that can bias the result have been taken into account, will the results be reliable. Here is one example of why some Gulf War research results may be contradictory:

As Steele showed, many nondeployed Gulf "era" veterans were given vaccinations in preparation for deployment, and these vaccinated "era" veterans reported multi-symptom illness at 3 times the rate of unvaccinated, nondeployed "era" veterans.

According to the military's Defense Medical Surveillance System (DMSS) raw data, soldiers vaccinated with anthrax vaccine have heart attacks at a greater rate than prior to vaccination. Thus, if deployed veterans are compared to a nondeployed group, of whom many received deployment vaccines, determining whether deployed veterans have more heart attacks than expected is confounded (made unreliable) by the nondeployed group's vaccinations.

Military and VA health databases have not been made available to independent researchers to study.

5. Has the health of Gulf War veterans improved over time?

Veterans who developed this syndrome have, for the most part, remained ill. Ten years later, one study found that 29% of deployed veterans had chronic, multi-symptom illness.

6. Do GW veterans die at a higher rate?

Three studies have demonstrated that GW veterans had an approximately 50% greater risk of accidental deaths, particularly from motor vehicle accidents. Although this has been attributed to elevated risk-taking behavior in deployed GW soldiers by some, others (including myself) suspect it is at least partly related to the cognitive problems faced by GW veterans, particularly their difficulties with attention and concentration.

One study found that testicular cancer rates were increased in Persian Gulf War veterans. This is usually a curable cancer that occurs in young males, so would not be expected to increase overall mortality rates significantly.

Other statistical studies have shown no more deaths and no more birth defects in offspring of GW soldiers than in comparable groups. However, was the control group truly comparable? Deployed troops are known to be much healthier than a group of age and sex-matched civilians, and this is commonly termed the "Healthy Warrior" effect. But they may also be healthier than the Gulf "era" troops who were not deployed, although "era" troops usually form the comparison group.

Steele showed that in Kansas veterans, the rate of multi-symptom illness varied by deployment location. Since different units had very varied exposures during their deployments, high rates of birth defects and/or deaths in certain units are possible. Yet the types of large epidemiological studies that have been performed have usually obscured possible localized effects of service in the Gulf.

7. Self reports

The validity of studies of GW veterans' health and exposures has been criticized on the basis that the exposure and illness data are reported by veterans, and not obtained from more reliable sources, such as military or VA databases. Some measures of current health could be obtained from those databases, but the data would be incomplete. Exposure data have not been a part of the available record for most veterans. Exposure data that have been supplied by DOD have been unreliable (in terms of the Khamisiyah plume modeling, according to GAO) or the data contradicted the self-reports (as in immunization data supplied by DOD to VA, following presentation of a VA study that linked anthrax vaccinations to subsequent ill health), or the data are missing or classified. The number, names and locations of all sites at which chemical warfare agents were exploded remain unknown to the public.

Are self-reports valid? Two recent studies indicate that GW veterans give reliable answers to questions. A study that compared GW veterans with Gulf era veterans' performance on neuropsychological examinations found that only 1% of GW veterans provided "noncredible" exams versus 4% of era veterans. Therefore, self-reports by GW veterans can safely be judged credible.

8. Why has the reality of Gulf War Syndrome been so contentious?

Perhaps remarks by Alabama Congressman Glen Browder in a 1993 House Armed Services Oversight and Investigations Subcommittee meeting shed some light on this:

"I have asked a lot of questions about why the Pentagon continues to stonewall these Gulf War veterans, or why are they so resistant to full and open examination of this problem. I don't have any conclusive answers but I can speculate.
First, it may be pride. To acknowledge these mystery casualties may blemish our Persian Gulf victory. Or, such an acknowledgement may be a terrifying admission that the United States did not and perhaps cannot protect our military men and women against chemical and biological warfare.
But I personally suspect that dealing openly and fully with these mystery ailments, and therefore the dirty little secret, will require the Pentagon to make budgetary and programmatic adjustments that it does not want to make."

Military doctrine calls for continuing use of anthrax and smallpox vaccines, multiple simultaneous vaccinations, pyridostigmine bromide tablets for prophylaxis of nerve gas exposure and depleted uranium munitions and armor. Thus military studies that concluded these exposures were safe should come as no surprise. Yet evidence of their adverse effects on health is abundant.

The American Type Culture Collection (ATCC) supplied various microbial cultures to Iraq, in shipments approved by the Department of Commerce, during a period in which the United States assisted Iraq in its war with Iran. This may have influenced why infections due to Brucella melitensis, one of the bacteria provided to Iraq, were not investigated. Vollum strain anthrax (which had been weaponized by the US military before the Biological Weapons Convention came into force in 1975) was provided to Iraq by ATCC. Knowing a US corporation provided Iraq virulent anthrax (not a strain used to make vaccines) may have influenced the defense department's decision to vaccinate troops against anthrax. Similarly, the ATCC provided Clostridium botulinum to Iraq; some soldiers were later vaccinated for potential exposure to botulinum toxins.

Admitting that soldiers became ill as a consequence of what the US gave Iraq may be politically unacceptable, undermining the likelihood that credible scientific studies of these exposures, funded by the government, would be performed.

According to the House Committee on Government Reform and Oversight in 1997,

"VA medical policy may have been biased against findings of chemical exposure by relying on DOD assertions and unproven theories of toxic causation. VA continues today to maintain that chronic symptoms in Gulf War veterans cannot be attributed to toxic exposures unless acute symptoms first appear at the time of exposure."

Yet the requirement for acute symptoms to occur in order to be harmed by chemical weapons (organophosphates) is scientifically insupportable.

Investigating certain GW exposures has been a career killer. While some researchers were amply rewarded for finding stress/psychological causes for Gulf War Illnesses, other researchers were punished for exploring politically unacceptable causes:

- Jim Moss, PhD on pyridostigmine potentiation research: "Middle and upper level management at USDA promised me I would be blackballed if I did not stop the research, or if I ever disclosed my research to anybody (this was before I appeared before the Senate VA committee). My biggest regret from my 1994 Senate VA committee testimony has been that I did not tell the committee about the threats."
- Charles Gutierrez, MS found microorganisms resembling Brucella melitensis in stools of dozens of Gulf War veterans in Tennessee, but had his studies halted: "In the years following the Persian Gulf War, extensive clinical studies on samples from Persian Gulf War veterans were performed at the James Quillen VA in Mountain Home, Tennessee. This work was not adequately pursued by the VA, and was instead ordered stopped. The findings in these patients need to be addressed, as they may fill in gaps in the existing body of GW illness research."

• Garth Nicolson, PhD on mycoplasma studies: " I was told by the President of my institution (the Univ. of Texas M.D. Anderson Cancer Center) to stop my GWI research or face disciplinary action. I refused to stop my research, and my professional career, academic position (and any possible future academic position) were destroyed by character assignation and outright lies about my research activities. This occurred even though our work was published in peer-reviewed academic journals. This was described in our book Project Day Lily (www.projectdaylily.com)."

9. How is it that Federal public health "watchdog" agencies and oversight mechanisms failed to prevent the public health disaster of GWS?

Federal agencies that could have weighed in on the safety of drugs and vaccines given to soldiers in the Gulf have become politicized, and their decision-making processes are opaque. The regulation of toxic substances is fragmented, overseen by a variety of agencies. Recent FDA decisions, and the agency's structure, suggest safety has a low priority.

- FDA permitted use of unlicensed drugs and vaccines, and use of licensed products for unproven purposes, during the Gulf War and later
- FDA repeatedly approved anthrax vaccine use for bioterrorism preparedness in the absence of required human data demonstrating effectiveness, and despite ample evidence of safety concerns
- Astonishingly, FDA drug and vaccine safety experts have no regulatory authority
- FDA "safety experts work largely in isolation, with limited resources and outdated technology."
- "The FDA has bungled its effort to build a new system for detecting the side effects of medicines after they go on the market, delaying its implementation by at least four years, according to a report commissioned by the agency itself... the FDA has wasted an estimated $25 million on its efforts."

- CDC continues to misinform recipients of anthrax vaccine with an official Vaccine Information Statement affirming vaccine safety that is in conflict with the vaccine's FDA-approved package insert, and what CDC officials told GAO about adverse events following vaccination. The GAO, citing CDC and Vaccine Healthcare Center officials as sources, reported that 1-2% of anthrax-vaccinated individuals "may experience severe adverse events, which could result in disability or death," in June 2007.
- CDC conducted a trial of anthrax vaccine in 1564 people beginning in 2002 and provided an interim report on the study to FDA. Yet CDC has released no information to the public about the trial findings, despite filing over 100 adverse event reports on trial subjects to the Vaccine Adverse Event Reporting System.
- These federal agencies know that injured military servicemembers are prevented by the Feres Doctrine from seeking a remedy for their injuries through the legal system.

• There are no viable legal remedies to hold military or government personnel accountable for deliberate cover-ups resulting in denial of healthcare and disability benefits mandated by federal law.

9. What Gulf War exposures did soldiers face, and what do we know about the injuries they may cause?

a) Depleted uranium (DU)

DU is comprised of uranium that has had 40% of its radioactive isotope, uranium-235, extracted. However, the DU used by the United States military also contains "recycled" nuclear reactor waste, including small amounts of highly radioactive plutonium-239, neptunium-237, technicium-99, americium etc.

Both munitions and armor may be made from DU. When a DU munition strikes an object, or when DU armor is struck, it ignites and up to 50% of its mass can aerosolize into minute particles that may be inhaled and will contaminate the area for the foreseeable future. Inhaled DU may have prolonged retention in the lungs, accumulates in specific brain regions (in rat experiments) and settles in bone. Inhaled DU led to behavioral effects in animals. It is excreted by the kidneys. Its toxicity is both chemical and radiological.

The only veterans who have been studied longitudinally for DU exposure comprise a small group with embedded DU shrapnel. They have shown limited findings of genotoxicity and are otherwise well, but have a "relatively low uranium burden compared to historical uranium-exposed controls." However, other veterans with inhalation exposures are probably at greater risk of DU toxicity. One study found that reported exposure to DU doubled the risk of dying from disease. (Reported pesticide exposure in this study doubled the likelihood of accidental death.)

Consider that the recycled nuclear materials added to DU may not be evenly dispersed. If so, there are likely some veterans with greater exposure to highly radioactive materials, who are at increased risk of cancers, immune and reproductive effects. Recent evidence also points to uranium as an endocrine disruptor.

If we review the health of workers in uranium processing plants, we can obtain clues about what to expect in DU-exposed veterans. Uranium workers have had elevated rates of cancers, especially kidney and respiratory tract cancers. They also had elevated levels of chronic kidney disease.

The Energy Employee Occupational Illness Compensation Program Act of 2000 (P.L. 106-398) established a "special cohort" of workers employed at three Department of Energy uranium gaseous diffusion plants and Alaska's nuclear test site: because of the absence of exposure records, and the presence of ultra hazardous workplace exposures, the burden of proof has been shifted to the government for ill workers at these facilities. The combination of an ultra hazardous workplace and absent exposure records mirrors the plight of Gulf War veterans, and suggests to us that burden of proof requirements could be changed for veterans who suffer from illnesses characteristic of their toxic exposures.

b) Sarin

Sarin is an organophosphate "nerve" agent or anticholinesterase, which leads to excessive accumulation of the neurotransmitter acetylcholine at nerve synapses. It is in the same family as pesticides such as parathion and malathion. A recent study found a significant association between levels of estimated sarin/cyclosarin exposure and reduced white matter in the brain. The same researchers also found that "Sarin and cyclosarin exposure was associated with less proficient neurobehavioral functioning on tasks involving fine psychomotor dexterity and visuospatial abilities 4-5 years after exposure."

According to the Congressional Office of Technology Assessment (OTA) in 1990:

"Of particular concern are the delayed neurotoxic effects of some of the organophosphorous (organophosphate) insecticides. Some of these compounds cause degeneration of nerve processes in the limbs, leading to changes in sensation, muscular weakness and lack of coordination. Because of this property, the EPA requires that organophoshorous insecticides undergo special testing for delayed neurotoxicity."

Thus despite claims by DOD that lack of acute sarin toxicity precluded later disease, it was common knowledge at the time of the 1991 Gulf War that delayed adverse effects do occur from exposure to this class of compounds.

Furthermore, a VA study of mortality in 100,000 veterans said to be exposed to sarin at Khamisiyah found a statistically significant doubling of deaths from brain cancer in the exposed group, compared to unexposed Gulf War veterans, as well as a limited dose-response relationship.

According to a popular toxicology textbook, anticholinesterases may cause "drowsiness, lethargy, fatigue, mental confusion, inability to concentrate, headache, pressure in head, generalized weakness."

c) Other pesticides

Carbamate pesticides were used in the Gulf and also cause acetylcholine accumulation. They would augment the adverse effects of sarin and organophosphate insecticides. Organochlorine and pyrethrin insecticides have different mechanisms of action, but are also toxic to the peripheral and central nervous system, so their adverse effects might compound those of the acetylcholinesterases. Some pesticides have adverse immunotoxic effects as well. A recent review by NIH's National Institute of Environmental Health Sciences researchers discussed the state of knowledge of pesticide toxicity, and suggested that general malaise associated with mild cognitive dysfunction may be a sensitive marker for pesticide neurotoxicity.

d) Organic Solvents

These include jet and vehicle fuels, some cleaning agents and other industrial chemicals. According to the Office of Technology Assessment:

"Acute exposure to organic solvents can affect an individual's manual dexterity, response speed, coordination and balance. Chronic exposure of workers may lead to reduced function of the peripheral nerves and such adverse neurobehavioral effects as fatigue, irritability, loss of memory, sustained changes in personality or mood, and decreased ability to learn and concentrate."

Therefore, sarin nerve gas, organophosphate and other pesticides, and solvents have the potential to induce the neurological and neurobehavioral effects seen in Gulf War veterans. This was known prior to the first Gulf War.

e) Endemic diseases and/or biological weapons exposures

It remains unknown whether troops faced any biological attacks. Exposure to novel microorganisms has never been ruled out. The role of infections endemic to the middle east in Gulf War Illnesses is also unknown. The following three microorganisms probably infected some Gulf War veterans, but other microorganisms may also contribute to GWI.

- Leishmaniasis, due to a parasite spread by the sandfly, is endemic in Iraq, but the visceral form of the disease is difficult to diagnose. Until better diagnostics are available, it is certain that cases will be missed. It can take months or even years to develop symptoms, and leishmaniasis may develop into a chronic, debilitating illness.
- Brucella melitensis is both endemic to Iraq and a potential biological warfare agent. It can cause a slowly developing, fatiguing illness with a variety of possible signs and symptoms, especially joint pain and fever. It is difficult to diagnose because standard tests usually miss it, so unless it is considered in the differential diagnosis and special tests ordered, it will be overlooked.
- Mycoplasmas have been linked to chronic multisymptom illnesses. They are widely distributed, and the known spectrum of clinical illness they cause continues to expand. A significant percentage of GW veterans have antibodies to mycoplasma.

f) Contaminated water

Possible contaminants include endemic or deliberately added microorganisms and petroleum products. Soldiers reported that some storage tanks supplying drinking water were also used for vehicle fuels, and the water contained fuel residues.

g) Smoke from oil well fires

Little reliable data on the contents and concentrations of materials comprising the oil well fire smoke is available. Toxic inhalants could have been burned deliberately by retreating Iraqi troops.

h) Pyridostigmine bromide (unlicensed use) a.k.a. PB, NAPPS

Also increases acetylcholine at nerve synapses; will augment the adverse effects of sarin, organophosphate and carbamate insecticides. Multiple studies have linked PB use to later illness in GW troops.

i) Other unlicensed drugs approved for use in the Gulf theater

- Centoxin (J5 monoclonal antibody), purchased by the military, prior to licensure of the drug, to treat sepsis in Gulf War veterans. Found later to increase mortality rates in treated patients. Never licensed.

• Ribavirin, purchased by the military for use in unspecified viral illnesses. Yet when used later as an experimental treatment for SARS, Ribavirin produced anemia, bradycardia and hypomagnesemia, increasing mortality. Other researchers later noted, "Ribavirin should not be used empirically for the treatment of viral syndromes of unknown etiology." Ribavirin also causes immunotoxicity. Its adverse reactions include fatigue and depression, which may persist after the drug is stopped.

j) Electromagnetic fields

Electromagnetic weapons, including high power microwaves, were used to disrupt and destroy Iraqi electronic systems. Generation of electromagnetic fields may have been used for other effects, and for communication. Whether electromagnetic fields contributed to illness is unknown, as are the types and magnitudes of the exposures. However, the European Union's European Environment Agency has just called for immediate action to reduce exposure to microwaves, following an international scientific review, which concluded that safety limits set for the radiation are "thousands of times too lenient."

k) Vaccines

- Botulinum toxoid vaccine, manufactured by Michigan Department of Public Health, meant to immunize against botulinum toxins. The toxins block neurotransmission, as does the toxoid. Never licensed. Very little known about safety or efficacy.
- Anthrax vaccine, licensed with inadequate data. Concentration increased 100 times due to manufacturing changes at the time of the Gulf War. Identified as a risk factor for Gulf War illnesses by multiple studies. The vaccine's package insert lists the CDC definition of

Gulf War Syndrome as a reported adverse event following anthrax vaccine. Many of the over 5,000 reports to the Vaccine Adverse Event Reporting System of FDA-CDC for anthrax vaccine indicate chronic illnesses whose symptoms resemble GWS. I have treated many soldiers who became ill following anthrax vaccine given since the 1991 Gulf War, and the majority experience cognitive impairment, generalized pain and fatigue, among other symptoms, meeting the CDC's case definition for GWS. See my testimony to the House Veterans Affairs Health Subcommittee for additional information.

• Multiple vaccines given together within a short time period. Are multiple simultaneous vaccinations dangerous? Although the question has been discussed by the Institute of Medicine, the Armed Forces Epidemiology Board and the British Ministry of Defense, they provide no conclusive answer. Studies of multiple vaccinations associated with Gulf War Illnesses have shown a positive, dose-response relationship, suggesting they did contribute to GWI. Soldiers engaged in Operation Iraqi Freedom have also reported Gulf War Illness-like disease following multiple vaccinations, with both acute and chronic effects. British military policy now separates anthrax and smallpox vaccinations from other vaccinations by at least 5 days.

10. What can we conclude about the exposures?

a) Several of the exposures can individually produce the symptoms GW veterans are experiencing. Injuries from these substances can affect cognition, emotion, motor and sensory function. These include sarin, pesticides, solvents, anthrax vaccine and some chronic infections, at a minimum.

b) Combined exposures to certain toxic substances (and simultaneous exercise) greatly magnify the potential for adverse reactions:

- Somani et al. Exercise plus Pyridostigmine Bromide amplified oxidative injury in skeletal muscle of mice.
- Abou-Donia et al. "These results suggest that exposure to real-life doses of malathion, DEET and permethrin, alone or in combination, produce no overt signs of toxicity but induce significant neurobehavioral deficits and neuronal degeneration in brain."
- McCain et al. "A significant increase in lethality occurred when PB, permethrin and DEET were given concurrently, when compared to expected additive values."

• Haley RW et al. "Some Gulf War veterans may have delayed, chronic neurotoxic syndromes from wartime exposure to combinations of chemicals that inhibit butyrylcholinesterase and neuropathy target esterase."

c) Multiple simultaneous vaccinations increased the risk of GWS.

d) For some other exposures, there is very little available information on toxicity.

e) Depleted uranium likely contributed to chronic illnesses (and deaths in soldiers tasked to clean up DU.)

f) Illnesses resulting from infections, electromagnetic fields, smoke, drugs and possibly other exposures have not been ruled out in GW veterans.

11. What is known about underlying pathology in GWS?

a) Autonomic nervous system function has been shown to be altered in Gulf War veterans in multiple studies, as has hypothalamic pituitary adrenal function.

b) Altered immune function reflects another aspect of this disorder for many veterans.

c) One's genes affect the speed of processing of toxic substances and later manifestation of toxic effects.

d) Gulf War soldiers encountered an unprecedented mix of noxious substances, which are known to cause neurological, immunologic and other adverse effects. Gulf War Illness research even suggests a dose-response relationship between some exposures and symptoms.

* A very reasonable hypothesis is that those who became ill reached a tipping point, where their body's ability to safely process the toxic materials they took in was exceeded. Chronic illness may have resulted from tissue damage (such as permanent loss of neurons) and/or persisting metabolic abnormalities, which have yet to be defined, but are suspected to include impaired oxidative phosphorylation and/or other fundamental changes in body chemistry that can affect multiple organ systems.

12. Why have we no effective treatment strategies 16 years after the end of the war?

VA Treatment Trials

- The original two VA treatment trials were exorbitantly expensive, particularly given the number of subjects and cost of the interventions. Failure to conduct additional treatment studies was rationalized by these trials' high cost.
- The mycoplasma/doxycycline trial was a "failed study" in that positive results seen at 3 and 6 months did not carry over to 9 and 12-month follow-up, possibly due to a high dropout rate. Yet it was not repeated with a larger number of veterans to reach a definitive conclusion regarding the benefit of antibiotic treatment.

• The cognitive behavioral therapy/exercise trial showed extremely modest gains and a high dropout rate; these treatments are known to be of little value in patients with chronic fatigue syndrome, and exercise can make them worse; yet cognitive behavioral therapy and exercise are primary treatments recommended for GW veterans, who have a high rate of chronic fatigue syndrome.

* We do not need to continue to examine whether the noxious exposures already studied can cause GWI. They can, and they did. And we should have expected it. Some people were genetically more susceptible; some people received more or larger exposures. The result is that many veterans became chronically ill.

The manner in which DOD and VA pursued GW research was flawed for a variety of reasons.

- A significant amount of research focused on stress or psychiatric causes of illness.
- Certain exposures were studiously avoided as objects of study.
- Methodologies chosen were sometimes inadequate to answer the questions posed.
- Exposure data provided by DOD to researchers was not necessarily accurate.

• Funded studies were not selected on the basis of whether they would lead to a treatment, or to a policy change to protect future soldiers. Instead, some might suspect the research was designed to avoid uncovering negative information regarding use of DU, pyridostigmine bromide and anthrax vaccine.

This review of some GWI research shows that completed research projects have:

- confirmed the symptoms of the illnesses
- identified specific neurological deficits in affected veterans and some of their anatomic/ physiologic correlates,
- provided partial information on rates of different GW-associated illnesses, and

• furthered our knowledge of the adverse effects caused by some noxious GW exposures, alone and in combination.

13. Where should the research go from here? How can we meld our research goals with the need to develop effective treatment strategies?

Infections (where a treatment payoff could be very large)

- Perform conclusive research to determine if GW veterans have untreated chronic infections. Utilize all modalities including microscopy, specialized cultures, serology, PCR, etc. Develop new diagnostics when needed, such as for visceral leishmaniasis.
- Also seek novel infections (biological agents), using above techniques, genetic techniques, monoclonal antibodies, etc.
- Perform empiric antibiotic trials in veterans who test positive, including a repeat trial of antibiotics for veterans with positive mycoplasma forensic PCR (the test used to screen veterans for the earlier trial).

Value for money

- A large number of small, inexpensive pilot studies should be funded instead of a few large, mainly epidemiologic studies; later give larger grants to those projects that show the most promise in terms of treatment strategies.
- Make the grant application process inclusive. Encourage clinicians who have been caring for GW veterans to participate. Reduce the complexity, time and cost needed to complete grant applications. Don't restrict VA research grants to VA employees, as has been the case: open the process to the best scientists and proposals.
- Note the low cost, excellent methodology, analysis and results of Lea Steele's Kansas veterans study, compared to numerous federally funded studies that cost at least ten times

more and yielded much less information. Use her strategies as a model for other studies: passion for the subject, careful use of funds, thoughtful design and analysis.
- The selection process for grants must be transparent, which has not previously been the case.

Promising areas-basic research

The underlying causes of all the multi-symptom syndromes remain unknown. It is very probable that the molecular and cellular origin of these syndromes will be the same, although they are likely triggered by a variety of noxious exposures combined with genetic susceptibility. Because together these syndromes affect an estimated 6 million Americans, research identifying their underlying causes will pay enormous dividends, and should point the way to more effective treatment and prevention strategies.

- Gene expression studies have the potential to identify fundamental physiological processes that have been altered. Genetic and proteomic studies of both predisposing gene patterns and protein differences between affected and unaffected veterans have already shown promise in pilot studies, and should be continued.
- Abnormal ion channel function may provide a conceptual and physiologic bridge between fatigue, neuropathies and motor neuron disorders like ALS, providing clues to why different disorders develop after similar exposures. It may also help explain episodic alterations in mental status, arrhythmias and epileptic seizures in veterans. Maintaining ion gradients across membranes requires a lot of cellular energy. This can potentially be improved with supplements that improve intracellular adenosine triphosphate (ATP) production and oral electrolytes.

Specific studies that could reap valuable rewards

- Detailed study of individual families, in which family members have developed illnesses similar to the ill veteran. An exhaustive search for microorganisms should be undertaken. Search for DU that may have been present on items that returned home with the veteran. Seek other toxics in the home as appropriate to illnesses. Investigate gene expression in these families.
- Study illnesses and mortality in selected units that have reported high death rates; try to recapture their locations, job descriptions and exposures when deployed.
- Collect several hundred very ill GW veterans and perform exhaustive investigations on them, followed by treatment trials.
- Investigate those hypotheses for which researchers were threatened or forced to end their studies. Investigate the electromagnetic field strengths and frequencies of all weapons, communications devices and other equipment that may have been used in the war, and try to determine which areas or units were exposed and estimate the magnitude of exposure.
- The choice of control groups in research is critical to a meaningful outcome: compare GW veterans with controls who did not receive deployment vaccines and had demonstrated equivalent health status. Review all research projects with independent experts prior to funding, to minimize confounding and bias.
- Eight expert committees have made recommendations on the research studies needed for anthrax vaccine since 1999. Their recommendations are excellent, and should be followed.

- Eight hundred Israeli soldiers received US anthrax vaccine or a similar Israeli anthrax vaccine several years ago, and dozens have reported chronic illnesses they believe are related to their vaccinations. Information from this trial should be obtained, along with follow-up examinations to document what illnesses, if any, have developed and rates of illnesses.
- A clinical trial of various strategies to remove toxic substances would be extremely useful. Do antioxidants, vitamins, saunas, or other strategies safely remove toxins after an exposure and lead to better health?

Obtain relevant information from existing government databases

- The Army Medical Surveillance Activity has performed many analyses of its raw data (the Defense Medical Surveillance System) on the health status of soldiers and GW veterans. These studies were not published, nor are they easily available. A researcher who filed Freedom of Information Act requests to learn what was studied, shared 66 pages with approximately 40 study titles listed per page with me. I have filed a Freedom of Information Act Request for the contents of 60 of these studies that pertain to the health of Gulf War veterans; my request is pending. Any serious study of Gulf War veteran health needs to make use of this material and the available military and VA databases. The Institute of Medicine noted that, "Analysis of DMSS data should be the primary approach for investigation of possible AVA (anthrax vaccine adsorbed)-related health effects of medical significance." This should be true of other potential health impacts, in addition to anthrax vaccine.
- VA and military databases, used correctly, can tell us which other illnesses can be linked to the Gulf deployment, and the strength of the association, so that appropriate presumptions can be made about the illnesses' cause; disability decisions can then be made based on presumption.
- Independent researchers who gain access to this data to study GWI, and determine what other illnesses may be linked with the 1991 Gulf War deployment, should not be subject to the military chain of command nor be VA employees.
- We can learn more about the health risks of toxic GW exposures by gaining access to data held by federal agencies. This includes obtaining information about anthrax vaccine adverse effects from FDA. What in-house studies or reviews have been done of anthrax vaccine? How has FDA evaluated the 5600 adverse event reports, particularly the 670 it judged serious? What assessment was done of the 44 reported deaths associated with anthrax vaccine? How is the vaccine tested for safety? (I filed several FOIAs with FDA for this information since 2001. So far, 99% of what I requested was redacted, and much has never been provided in any form. Yet the material should not have been withheld according to FDA guidelines (21 CFR20.61 and 21CFR601.51.)
- EPA and NIEHS have information about pesticide, heavy metal and solvent health risks. DOE has information on the makeup and production of depleted uranium. These sources of information should be explored for their potential to shed more light on the specifics of the illnesses causes by these materials.
- Anthrax vaccine trials: NIH has data on human trials of failed anthrax vaccines and CDC has data on its own clinical trial of 1564 subjects who received anthrax vaccine since 2002. What adverse events occurred in these carefully studied groups? What is the

current health of the subjects? Late follow-up could be done on these subjects to evaluate for longer-term adverse events.

- Multiple vaccines: Currently deploying soldiers are receiving multiple simultaneous vaccinations and should be studied.
- The military vaccine healthcare centers have data on over 2,000 soldiers who have become ill after anthrax vaccines. As well as documenting the illnesses in great detail, the centers have tried a variety of treatment regimens. Information on the illnesses and the effectiveness of the treatments is extremely relevant to GW veterans.

14. My medical approach to treatment

GWS is one of medicine's poor stepchildren for many reasons. Patients with memory and concentration problems require a lot more time and understanding from both physicians and clinic staff, compared to other patients. They miss appointments, lose prescriptions, forget the instructions you gave them. They have an average of eight different problems to address at each visit. They often have emotional issues. They are at high risk of family breakdown and economic collapse. Standard medications don't alleviate their symptoms. Providers may not understand their illnesses nor the context in which they seek care. They may be suspected as having secondary gain (desiring a disability pension) as the driver for medical visits. Yet sometimes almost the only thing the physician can do for the GWI patient is to aid the disability process by keeping detailed notes.

This syndrome is not described in textbooks. Journal articles may list the symptoms, but fail to guide clinicians with information on effective treatments. If the clinician reads the GWI literature, she may come away confused as to whether there really is a medical illness, and whether she should transfer the patient to the psychiatric clinic.

There are no standard medical treatments for the chronic effects of exposure to pesticides, solvents, toxic materials in inhaled smoke, etc. A few doctors have experimented with various detoxification strategies, and some alternative doctors use these treatments frequently, but they are not proven to be effective and are not eligible for third party reimbursement.

Medicine is a business. Third party payers use similar visit codes to reimburse physicians. Treating 4 patients in an hour pays much better than treating one. The maximal visit code pays for a 40 minute visit. Additional time spent with the patient will not be reimbursed. Extra time spent by office staff is not reimbursed. I am fortunate that as a salaried physician, my employer, Mount Desert Island Hospital, allows me to conduct a specialty clinic as a community service, even though I could bring in considerably more fees treating patients with standard illnesses during brief visits. Patients often travel long distances to see these doctors, who are few and far between. Thus they need long visits. Few GW veterans can afford to pay out of pocket for medical care, which is how most doctors who treat multi-symptom syndromes expect payment, because of the limitations placed on reimbursement by insurers.
Frankly, until the financial disincentive is changed, I doubt that treatment of GW veterans will improve greatly.

What do I actually do with patients? First, patients complete detailed questionnaires prior to their visit to help me determine which aspects of the illnesses are present in their case. Because

I am familiar with the features of the multisymptom syndromes, I know what to look for, ask about, and can direct treatment to these aspects of the illness. For example:

- Are they sensitive to odors (especially diesel exhaust), fluorescent lights or foods?
- What happens when exposed to these things?
- Do they have intermittent episodes of confusion?
- Do they balance their own checkbook?
- How is their driving?
- How is their GI tract function?
- How do they sleep? Has their partner noticed pauses in breathing?
- Do they have chronic pain? Where? What exacerbates or relieves it?
- What kind of activity can they perform? For how long? What makes them stop?
- Do they have rashes?
- How is their breathing?
- How is their libido and sexual function?
- Is there mold, or are there other substances at home or elsewhere that increase symptoms?

If they have developed multiple chemical sensitivity (which seems to be present in about 40% of GWS patients), I help them identify the odors that provoke symptoms so they can avoid them. I prescribe elimination diets to identify foods that trigger symptoms. I order tests to rule out other causes of symptoms, such as muscle diseases, standard autoimmune conditions, thyroid disease, anemia, etc. I may order sleep studies. Some patients may get a muscle biopsy or other specialized tests. Stools are cultured and endoscopy performed when indicated.

I then address treatment for each symptom individually, since we cannot currently address underlying causes. However, I additionally try to optimize patients' overall metabolic function with diet, vitamins and supplements designed to increase cellular energy and provide substrates for important intracellular molecules such as NADH, glutathione, ATP. Antioxidants may also be helpful. Most veterans cannot afford this treatment, however. Vitamins and supplements are not covered by insurance, although they are usually much cheaper than prescription medications.

Hopefully, clinical trials will demonstrate whether these approaches improve health, and if so, perhaps the VA will make vitamins and supplements available to GW veterans.

I treat the sleep disorder, diarrhea, pain, low hormone levels, or whatever other symptoms are present. I try one treatment after another, since there are many adverse reactions to medications, and it is often difficult to predict which medicines are likely to be effective. Usually, you can improve sleep considerably, but energy only a little. You can improve pain. The diarrhea can resolve, though it may return later. Sometimes sex hormones improve sexual function, but often they do not. Thyroid hormone may provide a modest energy boost. Autonomic dysfunction may be treated with increased salt and water intake, drugs and/or hormones to raise blood pressure, and electrolytes. If you are very lucky, cognition may improve.

The doctor-patient relationship, and lifestyle coaching, may be equally as important as medications. Patients need to know you are their partner, not a representative of a system they fear is pitted against them. I warn them that marital difficulties should be expected. I prefer

their partners to attend visits, and am happy to answer partners' questions. Treating psychological problems may be helpful, but veterans are sensitive that such treatment is a denial they have physical illness. I explain that they have real medical illness, and may give them an article or book on GWS that describes the resulting psychological and physical symptoms, to help them understand their disorder. I may refer to other therapists. I suggest that people with limited mental and physical energy reserve their most challenging tasks for when they feel most rested. I may advise them not to drive alone.

With this treatment, I estimate a veterans's overall function can improve 30-40% and sometimes more. But it is a piecemeal, palliative, symptom-based approach that does not provide a cure. It also requires highly intensive care. A list of many of the treatments I employ was provided to the VA Research Advisory Committee and listed on my website at: http://www.anthraxvaccine.org/gulfwartreatment.htm.

I greatly appreciate this opportunity to share my knowledge and opinions with the Committee.

I would also like to express my appreciation to Walter Schumm, PhD, Garth Nicolson, PhD, and affected Gulf War veterans Doug Rokke, PhD, Joyce Riley, RN and Kirt Love for sharing materials on GWS that were used in this presentation. My deepest thanks also to Lt. Col. John Richardson, retired Air Force GW veteran (still healthy), who has worked tirelessly to improve the condition of his fellow GW veterans and anthrax vaccine-injured soldiers.