Gulf War Illness and the Health of Gulf War Veterans:
Scientific Findings and Recommendations

Lea Steele, Ph.D.
Research Advisory Committee on Gulf War Veterans' Illnesses
November 17, 2008
Gulf War Illness and the Health of Gulf War Veterans: Scientific Findings and Recommendations

- Longstanding debate about Gulf War illness
  - Is it real?
  - Was it caused by stress? hazardous exposures? which exposures?
- Arguments for/against a specific “cause” of Gulf War illness have largely been based on conjecture. Suggestions that a particular substance could cause health problems often interpreted to mean that it did.
  - “Stress can have adverse health effects”
  - “Depleted uranium is radioactive”
  - “Intense oil fire smoke caused persistent cough”
- Early Gulf War review panels had little scientific evidence on which to base conclusions.
- 17 years after the war, this is no longer the case. Extensive amount of evidence of different types from many sectors

- This report is the first time this extensive evidence has been considered in aggregate, synthesized, to determine what is known about basic questions related to Gulf War illness.
- This evidence:
  - Provides consistent information re: the most prominent causes of Gulf War illness, and what did not cause Gulf War illness.
  - Provides important insights into the biological nature of Gulf War illness
  - Provides direction for additional research needed to improve the health of Gulf War veterans
Gulf War Illness and the Health of Gulf War Veterans: Scientific Findings and Recommendations

- Background: The 1990-1991 Gulf War and Gulf War Illness

- Key Findings of the Report
  - Impact, Characteristics of Gulf War Illness
  - What Caused Gulf War Illness?
  - Biological Characteristics of Gulf War Illness
  - Other Gulf War-related Health Issues
  - Federal Research on the Health of Gulf War Veterans
  - Recommendations

Guiding principle of the Committee’s work (by charter):

-- The fundamental goal of Gulf War research is to improve the health of ill Gulf War veterans --
The Gulf War and Gulf War Illness

Aug 2, 1990 - Iraq invaded Kuwait
Jan 16, 1991 - Air strikes began
Feb 24, 1991 - Ground combat began
Feb 28, 1991 - Cease fire declared

- 6 weeks air strikes, 4 day ground war
- "100 Hour War"
- ~697,000 U.S. troops deployed to region
- Decisive victory; relatively few casualties
- < 150 battle-related deaths
Gulf War Illness: Chronic Symptoms in the Wake of Desert Storm

Widespread reports of unexplained problems:

- Chronic headaches
- Widespread pain
- Memory and concentration problems
- Persistent, unexplained fatigue
- Mood changes
- Chronic diarrhea
- Respiratory problems
- Unusual skin rashes

Diverse Gulf War-related exposures of potential concern:

- Psychological stress
- Chemical weapons
- Oil well fires
- Munitions containing depleted uranium
- Heavy use of insecticides/repellants
- Pyridostigmine bromide pills (PB) to protect from nerve agents
- Vaccines
- Infectious diseases
- Tent heater exhaust
- High levels of airborne particulates
- Fuel exposures
- Solvents, CARC paint
What is Gulf War Illness, and what caused it?

What does the evidence show, 17 years after the war?
Gulf War Illness and the Health of Gulf War Veterans: Scientific Findings and Recommendations

Characteristics, Impact of Gulf War Illness

- **Characteristics of Gulf War Illness**
  - Many Gulf War veteran groups studied (many different units, all regions of U.S., some Coalition countries)
  - All identify significant excess of symptoms in Gulf War veterans, compared to nondeployed era veterans
  - Consistent types/patterns of excess symptoms identified statistically
    - Neuro/cognitive problems
    - Widespread pain
    - Unexplained fatigue/sleep disturbances
    - Gastrointestinal symptoms
    - Respiratory problems
    - Skin abnormalities
Gulf War Illness and the Health of Gulf War Veterans: Scientific Findings and Recommendations

- Neuro/cognitive problems
- Widespread pain
- Persistent, unexplained fatigue
- Gastrointestinal symptoms
- Respiratory problems
- Skin abnormalities

Gulf War Illness: How Many Veterans Are Affected?

- Multiple studies, identified rates differ with how GWI defined
- Compare levels of symptomatic illness in Gulf veterans and nondeployed era veterans; excess reflects the rate of illness attributable to service in the 1991 Gulf War (i.e., “Gulf War illness”)
- Studies consistently identify an excess of 26-32% of Gulf War veterans with multisymptom illness (over and above rates in nondeployed era veterans)
Gulf War Illness and the Health of Gulf War Veterans: Scientific Findings and Recommendations

- Gulf War Illness: Which Veterans are Most Affected?
  - Army has sign. higher rates than other branches; ground troops > Air Force, those on board ship
  - Differs by location during deployment (forward deployed > those in support areas, those at sea)
  - Enlisted personnel have sign. higher rates than officers
  - Little/no difference by gender, race, age
  - GWI rates differ significantly in relation to specific exposures during the war

Table 1. Prevalence of Multisymptom Illness in Gulf War Veterans and Nondeployed Era Veterans

<table>
<thead>
<tr>
<th>Veterans Studied</th>
<th>Number of Gulf War Veterans Assessed</th>
<th>Year(s) of Assessment</th>
<th>Case Definition Used</th>
<th>Prevalence in Nondeployed Veterans</th>
<th>Prevalence in Gulf War veterans</th>
<th>Excess Illness in Gulf War Veterans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air Force veterans</td>
<td>1,155</td>
<td>1995</td>
<td>CMI</td>
<td>15%</td>
<td>45%</td>
<td>30%</td>
</tr>
<tr>
<td>New England Army veterans</td>
<td>180</td>
<td>1994-1995</td>
<td>CMI (modified)</td>
<td>33%</td>
<td>65%</td>
<td>32%</td>
</tr>
<tr>
<td>U.K. male veterans</td>
<td>4,492</td>
<td>1998</td>
<td>CMI (modified)</td>
<td>90%</td>
<td>63%</td>
<td>27%</td>
</tr>
<tr>
<td>U.K. female veterans</td>
<td>226</td>
<td>1998</td>
<td>CMI (modified)</td>
<td>35%</td>
<td>64%</td>
<td>29%</td>
</tr>
<tr>
<td>Kansas veterans</td>
<td>1,546</td>
<td>1998</td>
<td>GWI (KS)</td>
<td>8%</td>
<td>34%</td>
<td>26%</td>
</tr>
<tr>
<td>U.S. national study, Phase III</td>
<td>5,095</td>
<td>1999-2001</td>
<td>CMI</td>
<td>16%</td>
<td>29%</td>
<td>13%</td>
</tr>
<tr>
<td>U.S. national study, sample</td>
<td>5,767</td>
<td>2005</td>
<td>Multisymptom Illness</td>
<td>10%</td>
<td>36%</td>
<td>25%</td>
</tr>
</tbody>
</table>

Abbreviations: CMI = chronic multisymptom illness as defined by Fukuda et al. (1993) Gulf War Illness = Gulf War Illness, KS = Kansas case definition
Notes: Multisymptom illness defined as multiple types of symptoms occurring together, not explained by medical or psychiatric diagnosis.
Gulf War Illness and the Health of Gulf War Veterans: Scientific Findings and Recommendations

- Gulf War Illness: Are Veterans Getting Better or Worse With Time?
  - All follow-up studies report that few veterans have recovered or substantially improved over time
  - VA National Longitudinal Study (5767 GW veterans, 10 years after initial survey): Of veterans with history of multisymptom illness: 2% recovered, 7% much improved, 15% much worse
  - No treatments have been identified that provide substantial benefit

- Gulf War Illness: Does the same thing happen after every war?
  - No. Studies have not identified Gulf War illness-type problem in relation to deployments since the Gulf War (Bosnia, Iraq, Afghanistan)
  - That is, no widespread problem with symptomatic illness not explained by medical or psychiatric diagnoses
Gulf War Illness and the Health of Gulf War Veterans: Scientific Findings and Recommendations

- Key Findings of the Report
  - Impact of Gulf War Illness
  - What Caused Gulf War Illness?
  - Biological Characteristics of Gulf War Illness
  - Federal Research on the Health of Gulf War Veterans
  - Recommendations

Diverse Gulf War-related experiences and exposures of potential concern

- Psychological stressors
- Chemical weapons
- Oil well fires
- Depleted uranium
- Heavy use of insecticides/repellants
- Pyridostigmine bromide pills
- Vaccines
- Infectious diseases
- Tent heaters
- Particulates
- Fuel exposures
- Solvents, CARC paint
What Caused Gulf War Illness?

What does the evidence show, 17 years after the war?

For Each Possible “Cause,” 3 Types of Evidence Considered

- What is Known About the Patterns and Extent of Exposure During Deployment
- General Research on Known Health Effects of Each Exposure
- Findings on Exposure Effects from Studies of Gulf War Veterans
What Caused Gulf War Illness?
For Each Possible “Cause,” 3 Types of Evidence Considered

Patterns and Extent of Exposure During Deployment
- Documented exposures, where available (e.g. stress, oil fires, vaccines, DU)
- Government investigations to determine types of exposures, extent and patterns of exposures
- Exposure modeling (using weather patterns, simulations, etc)
- Veteran-reported exposures in epidemiologic studies

Scientific Research on Known Health Effects of Exposure
- Human health effects in occupationally-exposed groups
- Human health effects related to general environmental exposures
- Laboratory studies in animals exposed to individual compounds, combined effects of multiple exposures

Findings on Exposure Effects from Studies of Gulf War Veterans
- Epidemiologic studies that evaluated rates of symptomatic illness in relation to deployment experiences and exposures
- Studies measuring objective clinical outcomes in relation to Gulf War exposures

Diverse Gulf War-related experiences and exposures of potential concern

- Psychological stressors
  - Chemical weapons
  - Oil well fires
  - Depleted uranium
  - Insecticides/ repellants
  - Pyridostigmine bromide pills
  - Vaccines
  - Infectious diseases
  - Tent heaters
  - Particulates
  - Fuel exposures
  - Solvents, CARC paint

- Serving in combat
- Seeing buddy killed, other casualties
- Being shot at
- Close to exploding SCUD
- Family problems back home
Diverse Gulf War-related experiences and exposures of potential concern

- Psychological stressors
- Chemical weapons
  - Modeled nerve agent releases
  - Wore gas mask during chemical alert
  - Experienced a likely chemical attack
  - Thought chemical agents were used
- Oil well fires
- Depleted uranium
- Insecticides/repellants
- Pyridostigmine bromide pills
- Vaccines
- Infectious diseases
- Tent heaters
- Particulates
- Fuel exposures
- Solvents, CARC paint
What Caused Gulf War Illness?

What does the evidence show, 17 years after the war?

Summary: What the Weight of Evidence Tells Us About the Causes of Gulf War Illness

- Psychological stress  Evidence consistently indicates no association
- Pyridostigmine bromide (PB)  Evidence consistently indicates a causal association
  - Pesticides
- Low-level nerve agents  Association cannot be ruled out; Some evidence supports an association, but evidence is inconsistent or limited in important ways
  - Sustained oil well smoke
  - Large number of vaccines
  - Combinations of exposures
- Depleted uranium  Unlikely to have caused Gulf War illness for the majority of affected veterans
  - Anthrax vaccine
  - Fuels, solvents
  - Sand, particulates
  - Other
Review of Evidence on the Causes of Gulf War Illness

- Psychological stress during deployment is NOT significantly associated with Gulf War Illness

  *Extensive information about psychological stressors during deployment*

  *Large number of studies have assessed effects of many types of psychological stressors on the health of Gulf War veterans*

  ✓ Studies consistently indicate that neither extreme trauma nor more moderate stressors during deployment are sign. risk factors for Gulf War illness

---

**Table 2. Participation in Combat as a Risk Factor for Chronic Symptoms and Multisymptom Illness in Gulf War Veterans**

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample</th>
<th>Combat Association Evaluated</th>
<th>Unadjusted Association</th>
<th>Association Adjusted For Other Exposures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cherry²⁰¹¹ 2001</td>
<td>7,971 U.K. Gulf War vets</td>
<td>Correlation of combat with seven symptom domains, overall symptom severity, peripheral neuropathy, widespread pain</td>
<td>Not reported</td>
<td>None significant</td>
</tr>
<tr>
<td>Gru²⁰²    2002</td>
<td>3,831 Navy Seabees</td>
<td>Combat as a risk factor for study-defined Gulf War illness</td>
<td>OR = 2.5*</td>
<td>Not significant</td>
</tr>
<tr>
<td>Nisenbaum²⁰³ 2000</td>
<td>1,002 Air Force vets</td>
<td>Combat duty in relation to severe or mild-moderate CMI</td>
<td>Not significant</td>
<td>Not significant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Coming under attack in relation to severe or mild-moderate CMI</td>
<td>OR (severe) = 2.4*</td>
<td>OR (severe) = 1.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OR (mild-moderate) = 1.1</td>
<td>OR (mild-moderate) = 0.7</td>
</tr>
</tbody>
</table>

Abbreviations: OR = odds ratio, CMI = chronic multisymptom illness

* = statistically significant
Review of Evidence on the Causes of Gulf War Illness

- Psychological stress during deployment is NOT sign. associated with Gulf War Illness

  ✓ Wartime trauma, stress consistently associated with increased rates of PTSD in Gulf War veterans, but not Gulf War illness

  ✓ Overall, PTSD rates in Gulf War veterans are lower than in veterans of other wars

Table 3. Prevalence of Clinically Diagnosed Post Traumatic Stress Disorder in Gulf War and Nondeployed Gulf War Era Veterans

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample</th>
<th>PTSD Measure</th>
<th>PTSD Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Gulf War</td>
<td>Nondeployed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Veterans</td>
<td>Veterans</td>
</tr>
<tr>
<td>Population-based sampling</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blanchard [10]</td>
<td>2,189 U.S. vets</td>
<td>CIDI</td>
<td>3.3%</td>
</tr>
<tr>
<td>Toomey [11]</td>
<td></td>
<td>CAPS</td>
<td>6.2%</td>
</tr>
<tr>
<td>Ikim [12]</td>
<td>2,758 Australian vets</td>
<td>CIDI</td>
<td>5.1%</td>
</tr>
<tr>
<td>Wolfe [13]</td>
<td>252 U.S. Army vets</td>
<td>CAPS, SCID</td>
<td>5.4, 7.2%</td>
</tr>
<tr>
<td>Gulf War Registries</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Engel [14]</td>
<td>21,232 U.S. vets in CCEP</td>
<td>Clinical</td>
<td>5.6%</td>
</tr>
<tr>
<td>VA [15]</td>
<td>70,395 U.S. vets in VA Registry</td>
<td>Clinical</td>
<td>3.8%</td>
</tr>
<tr>
<td>Lee [16]</td>
<td>3,223 in U.K. MAP</td>
<td>Clinical</td>
<td>12.0%</td>
</tr>
</tbody>
</table>

Abbreviations: CCEP = OOD Comprehensive Clinical Evaluation Program, MAP = British Medical Assessment Program, CIDI = Composite International Diagnostic Interview, CAPS = Clinical Assessment of PTSD, SCID = Structured Clinical Interview for DSM-III-R.
Review of Evidence on the Causes of Gulf War Illness

- **Pyridostigmine bromide (PB) use during deployment is causally related to Gulf War illness**
  - GW studies consistently identify PB to be a significant risk factor for Gulf War illness
  - Multiple studies have identified PB dose-response effects
  - PB side effects during deployment are significantly associated with increased rate of Gulf War illness
  - Objectively measured neurocognitive, endocrine differences related to PB use in the Gulf War
  - Autonomic alterations in humans with sustained, repeat exposure
  - Diverse neurological effects in animal models with sustained, repeat exposure
  - PB is an anticholinesterase compound, acts by the same mechanism as pesticides, nerve agents

- **Pesticide exposure during deployment is causally related to Gulf War illness**
  - **DOD reports:** 64 pesticide products used; 15 identified as “pesticides of concern;” at least 43,000 troops overexposed
  - GW studies consistently identify pesticides to be a significant risk factor for Gulf War illness; 2 studies identified dose-response effects
  - Studies have identified neurocognitive, endocrine differences related to pesticide use in the Gulf War
  - Pesticides are neurotoxicants, act by the same mechanism as PB and nerve agents
  - In other human populations, repeated or sustained low-level pesticide exposure has been associated with symptoms similar to Gulf War illness
  - Diverse neurological effects identified in animal models with repeated, low-level pesticide exposures
Summary: What the Weight of Evidence Tells Us About the Causes of Gulf War Illness

- Pyridostigmine bromide (PB)
  - Evidence consistently indicates a causal association

- Pesticides
  - Evidence consistently indicates no association

- Psychological stress
  - Association cannot be ruled out; Some evidence supports an association, but evidence is inconsistent or limited in important ways

- Low-level nerve agents
- Sustained oil well smoke
- Large number of vaccines
- Combinations of exposures

- Depleted uranium
- Anthrax vaccine
- Fuels, solvents
- Sand, particulates
- Other

Unlikely to have caused Gulf War illness for the majority of affected veterans
Gulf War Illness and the Health of Gulf War Veterans: Scientific Findings and Recommendations

- Key Findings of the Report
  - Impact of Gulf War Illness, other Gulf War-related health issues
  - What Caused Gulf War Illness?
  - Biological Characteristics of Gulf War Illness
  - Federal Research on the Health of Gulf War Veterans
  - Recommendations

Biological Characteristics of Gulf War Illness

What does the evidence show, 17 years after the war?
Biological Characteristics of Gulf War Illness: Diverse differences, most prominently relate to neurological function

Studies indicate that Gulf War illness is associated with significant differences in:

- Brain structure and function
- Autonomic nervous system function
- Hypothalamic-pituitary-adrenal measures
- Immune function
- Measures indicative of vulnerability to neurotoxicants

Table 2: Published EEG and Brain Imaging Findings in Symptomatic Gulf War Veterans

<table>
<thead>
<tr>
<th>Study</th>
<th>Group Studied</th>
<th>Method(s)</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Okate</td>
<td>20 symptomatic GW veterans in the UK GWVF</td>
<td>EEG, CT, MRI, PET</td>
<td>Results reported as “no evidence of any neurological disorder” specific measures not provided.</td>
</tr>
<tr>
<td>Balazs</td>
<td>2014</td>
<td>10 symptomatic GW, 5 non-symptomatic GW, veterans controls.</td>
<td>PET</td>
</tr>
<tr>
<td>Cohn</td>
<td>2009</td>
<td>27 symptomatic GW, 15 non-symptomatic GW</td>
<td>PET</td>
</tr>
<tr>
<td>Spanier</td>
<td>2006</td>
<td>21 GW with history of symptoms, 17 control (6 GW, 8 non-GW)</td>
<td>fMRI, fNIRS</td>
</tr>
</tbody>
</table>

### Biological Characteristics of Gulf War Illness

#### Brain structure and function: Neuroimaging Studies

<table>
<thead>
<tr>
<th>Evaluation Method</th>
<th>Results Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>H&lt;sub&gt;1&lt;/sub&gt;MRS, SPECT, MRI volume assessment</strong></td>
<td>Significant differences identified in 6 of 7 studies</td>
</tr>
<tr>
<td>Standard neuro exam, EEG, MRI, CT scans</td>
<td>No differences identified (0 of 4 studies)</td>
</tr>
</tbody>
</table>

#### Results Summary (symptomatic Gulf War veterans vs. controls)

**Method**
- **Neuroimaging**
  - **H<sub>1</sub>MRS**
  - **SPECT**
  - **MRI**

**Key Findings**
- Significant differences identified in 6 of 7 studies

---

### Table 4. Neurocognitive Evaluations of Gulf War-Deployed Veterans Overall, Not Differentiated by Veteran Health Status

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldstein&lt;sup&gt;20&lt;/sup&gt; 1996</td>
<td>31 GWV, 38 controls</td>
<td>GMV had lower overall test performance, as measured by global neuropsychological index based on 14 subtests. No sign. differences on individual tests. Adapted for psychological correlates, residualized eliminating group differences.</td>
</tr>
<tr>
<td>Austin&lt;sup&gt;21&lt;/sup&gt; 1997</td>
<td>44 males GWV from Army, 40 controls</td>
<td>Compared to normative values, GMV had lower skills on measures of motor speed and immediate memory.</td>
</tr>
<tr>
<td>Silberman&lt;sup&gt;22&lt;/sup&gt; 1997</td>
<td>44 GWV from single naive reactor setting</td>
<td>No sign. task performance effects seen with emotional dysphoria.</td>
</tr>
<tr>
<td>Linderholm&lt;sup&gt;23&lt;/sup&gt; 2000</td>
<td>44 subjects, 11 veterans</td>
<td>LTV tasks showed higher levels of deficits in attention and executive functioning are insidious. They need longer to screen affected tasks after controlling for multiple comparisons and psychosomatic diagnoses.</td>
</tr>
<tr>
<td>Linderholm&lt;sup&gt;24&lt;/sup&gt; 2003</td>
<td>In GMV, sign. cor. bet. TFC-7A severity and poorer performance on tasks of verbal ability. Combined tasks did not show any sign. differences in veterans who denied the to meningitis.</td>
<td></td>
</tr>
<tr>
<td>Linderholm&lt;sup&gt;25&lt;/sup&gt; 2003</td>
<td>Signs were neurocognitive symptoms reported by GWV veterans depressed Nikolaus 1999, GWV veterans symptom rate sign. associated with performance on tasks of verbal ability. Combined tasks did not show any sign. differences in veterans who denied the to meningitis.</td>
<td></td>
</tr>
<tr>
<td>Deer&lt;sup&gt;26&lt;/sup&gt; 2002</td>
<td>300 GWV/OEF, 75 controls</td>
<td>GMV had sign. lower performance on tests of verbal and nonverbal performance. No sign. differences in ages. Depression, education, were sign. and health were sign. controlled.</td>
</tr>
<tr>
<td>Gray&lt;sup&gt;27&lt;/sup&gt; 2002</td>
<td>5-85 GWV veterans, 4-85 healthy对照 veterans, 1-8 in all moderate TFC scores than after two groups on Cognitive Failure's Inhibitions.</td>
<td></td>
</tr>
<tr>
<td>Vandenberg&lt;sup&gt;28&lt;/sup&gt; 2002</td>
<td>70 GWV, 33 healthy veterans</td>
<td>No sign. differences on neuropsych measures.</td>
</tr>
<tr>
<td>Proctor&lt;sup&gt;29&lt;/sup&gt; 2002</td>
<td>140 GWV/OEF, 72 controls</td>
<td>No sign. differences on neuropsych tests. GMV reported higher mean recall.</td>
</tr>
<tr>
<td>Vihallenger&lt;sup&gt;30&lt;/sup&gt; 2004</td>
<td>14 GWV with PFSO, 22</td>
<td>No sign. differences associated with PFSO and Gulf War deployment.</td>
</tr>
<tr>
<td>GMV with PFSO, 22</td>
<td>GMV without PFSO, 20</td>
<td>No sign. differences between veterans. No sign. differences on measures of visuo-spatial and verbal memory.</td>
</tr>
<tr>
<td>Barlow&lt;sup&gt;31&lt;/sup&gt; 2007</td>
<td>307 GWV, 66 healthy veterans</td>
<td>Only 7% of GMV had sign. differences in patients. No sign. differences in patients. No sign. differences in patients.</td>
</tr>
</tbody>
</table>

*Note: GWV = Gulf War veterans, OEF = Operation Enduring Freedom, PFSO = post-deployment symptoms, ag = age, TFC = traumatic brain injury.*
Biological Characteristics of Gulf War Illness

Brain structure and function: Neurocognitive Studies

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Results Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic GW veterans vs. healthy controls</td>
<td>Sign. differences consistently identified (measured decrements in memory, attention, response speed, executive function, mood)</td>
</tr>
<tr>
<td>Neurocognitive function in relation to Gulf War exposures</td>
<td>Sign. differences associated with exposure to nerve agents (modeled), PB, pesticides</td>
</tr>
<tr>
<td>GW deployed vs. nondeployed veterans</td>
<td>Few differences identified</td>
</tr>
</tbody>
</table>

Table 4: Published Studies of Autonomic Function in Symptomatic Gulf War Veterans

<table>
<thead>
<tr>
<th>Study</th>
<th>Group Studied</th>
<th>Autonomic Tests</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhou et al., 2000</td>
<td>14 GWI with chem. and/or physical injury vs. 14 healthy controls</td>
<td>HSE - hot stand</td>
<td>Significantly higher mean heart rate at 15 and 30 min. than in healthy controls.</td>
</tr>
<tr>
<td>Park et al., 2002</td>
<td>40 GWI vs. 40 healthy controls</td>
<td>Cold pressor test and handgrip test</td>
<td>Significantly higher mean heart rate and systolic blood pressure in GWI compared to healthy controls.</td>
</tr>
<tr>
<td>Sand et al., 2002</td>
<td>35 symptomatic GWI vs. 35 healthy controls</td>
<td>RH - right handgrip, left handgrip</td>
<td>Fewer differences in autonomic function between groups.</td>
</tr>
<tr>
<td>Kato et al., 2004</td>
<td>30 GWI vs. 30 healthy controls</td>
<td>Deep breath challenge</td>
<td>Fewer differences in autonomic function between groups.</td>
</tr>
<tr>
<td>Stoel et al., 2004</td>
<td>11 GWI with chem. and/or physical injury vs. 11 healthy controls</td>
<td>24-hour ambulatory blood pressure monitoring</td>
<td>Fewer differences in autonomic function between groups.</td>
</tr>
<tr>
<td>Nava et al., 2004</td>
<td>22 GWI with injury vs. 22 healthy controls</td>
<td>24-hour ambulatory blood pressure monitoring and ECG</td>
<td>Fewer differences in autonomic function between groups.</td>
</tr>
<tr>
<td>Lussier et al., 2005</td>
<td>40 GWI vs. 40 healthy controls</td>
<td>24-hour ambulatory blood pressure monitoring and ECG</td>
<td>Fewer differences in autonomic function between groups.</td>
</tr>
</tbody>
</table>
Biological Characteristics of Gulf War Illness

Neurological function: Autonomic Nervous System (ANS) Function

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Results Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ANS evaluations</td>
<td>Sign. ANS differences in symptomatic GW veterans in 8 of 9 studies</td>
</tr>
<tr>
<td>Tilt testing, 24 hour electrocardiogram</td>
<td>Sign. differences in 6 of 6 studies</td>
</tr>
<tr>
<td>Valsalva maneuver, standing ratio, sympathetic skin response</td>
<td>No differences in 4 of 4 studies</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Group Studied</th>
<th>Parameter/Assay</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haley et al. 1995</td>
<td>2D-5D GW controls, 10 well GW controls, 8 nondeployed era controls</td>
<td>PON1 genotype [positions 152 and 155], enzyme activity in paracrine and conversion</td>
<td>GWV with hypothyroidism sign. more likely to have PON1 R allele than controls. No sign. differences in L, H alleles. Mean PON1 activity nonsign. Higher in cases, mean enzyme activity nonsign lower in cases; type C enzyme activity sign. Lower in cases, lower C-enzyme activity also sign. Associated with having more severe side effects from PB during deployment.</td>
</tr>
<tr>
<td>Masden et al. 2000</td>
<td>152 GWV with self-reported GW, 152 nonveteran controls</td>
<td>PON1 genotype, positions 152 and 155, serum PON1 concentration, enzyme activity in paracrine and conversion</td>
<td>GWV with GWV had sign. lower PON1 concentration and activity in paracrine than controls (activity = 50% of control), overall and within genotype. No differences in L, H gene frequencies or L, H frequencies in cases vs. controls. No differences in PON1 activity in patients.</td>
</tr>
<tr>
<td>Hagle et al. 2003</td>
<td>105 6'0' GWV, 8'7' GWV controls, 127 6'0' nondeployed era GWV and 127 controls</td>
<td>PON1 genotype, positions 152 and 155, enzyme activity in paracrine and conversion</td>
<td>Sign lower proportion of 8'7 then well GWV had L1 genotype (position 55). Overall, GWV-deployed test signifies lower PON1 activity than in GWV veterans. No sign. PON1 activity difference between 6'0' and well GWV.</td>
</tr>
<tr>
<td>Corcoran et al. 2007</td>
<td>110 male GWV with CM, 111 male GWV controls, 80 nondeployed era veterans (29 with CM)</td>
<td>PON1 activity [substrate tet</td>
<td>No sign. difference in adjusted mean difference of PON1 activity between cases and controls, or in deployed vs. nondeployed veterans.</td>
</tr>
</tbody>
</table>

*GWV = Gulf War veteran, GW = Gulf War illness, CM = Gulf War illness with chronic lymphoma, PB = pyridoxine, sign = statistically significant.*
## Biological Characteristics of Gulf War Illness

### Vulnerability to Neurotoxicants

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Results Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>PON1 enzyme activity (neutralizes effects of neurotoxicants)</td>
<td>Significant differences associated with Gulf War illness or Gulf War service, overall, in 5 of 6 studies</td>
</tr>
</tbody>
</table>

### Neuroendocrine function: Hypothalamic-Pituitary Adrenal (HPA) Measures

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Results Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPA measures on GW veterans vs. nondeployed veterans</td>
<td>Unique profile of HPA differences on multiple HPA measures in response to adrenal challenge; sign. difference on 24-hour cortisol, ACTH</td>
</tr>
<tr>
<td>Resting cortisol, ACTH</td>
<td>No differences</td>
</tr>
<tr>
<td>HPA measures in relation to PTSD, combat stress</td>
<td>No differences</td>
</tr>
</tbody>
</table>
Biological Characteristics of Gulf War Illness

Immune function

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Results Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circulating levels of inflammatory cytokines</td>
<td>Sign. increases in IFN-gamma, IL-4, IL-10 in symptomatic GW veterans in 2 of 2 studies</td>
</tr>
<tr>
<td>NK cells</td>
<td>Sign. reduced NK cell number and/or activity in symptomatic veterans in 3 of 4 studies</td>
</tr>
<tr>
<td>Immune competence in infection response</td>
<td>No differences in 4 of 4 studies</td>
</tr>
<tr>
<td>ANA, ESR</td>
<td>No differences in 3 of 3 studies</td>
</tr>
</tbody>
</table>

Biological Characteristics of Gulf War Illness:
Diverse differences, most prominently relate to neurological function

- Brain structure and function
- Autonomic nervous system function
- Neuroendocrine (hypothalamic-pituitary-adrenal) measures
- Measures indicative of vulnerability to neurotoxicants
- Immune function
Gulf War Illness and the Health of Gulf War Veterans: Scientific Findings and Recommendations

Other Gulf War Health Issues

Diagnosed Diseases
- ALS (Lou Gehrig’s disease) identified in GW veterans at twice the rate of other veterans
- Brain cancer deaths twice as high in GW veterans potentially exposed to nerve gas
- Rates of other cancers, neurological diseases, other diagnoses not known
- Epi studies suggest possible increase in migraines, asthma, gastrointestinal and skin conditions

Mortality Rates
- No published info after 1997 for overall mortality, disease-specific mortality
Other Gulf War-related health issues of importance

Health of Veterans' Children and Other Family Members

- Several large studies have identified increases in different types of birth defects in children of GW veterans, compared to nondeployed veterans (still within general population range)
- No published studies re: other health issues in veterans’ children
- One large study suggests no excess health problems in GW veterans’ spouses

Gulf War Illness and the Health of Gulf War Veterans: Scientific Findings and Recommendations

- Key Findings of the Report
  - Impact of Gulf War Illness
  - What Caused Gulf War Illness?
  - Biological Characteristics of Gulf War Illness
  - Federal Research on the Health of Gulf War Veterans
  - Recommendations
Federal Research on the Health of Gulf War Veterans

- 1994 - 2007: 345 individual projects, $340-442 million funding identified as “Gulf War Research” by federal agencies
- Historically, use of funds problematic
  - Substantial amount of funding for projects with little/no relevance to the health of Gulf War veterans
  - Substantial funding for studies of stress, psychiatric disease
- Federal Gulf War research programs have not yet improved the health of Gulf War veterans

Federal Research on the Health of Gulf War Veterans

- Recent changes at both DOD and VA represent promising new directions in federal Gulf War research
  - DOD CDMRP program focused on identifying treatments and diagnostic tests
  - VA-funded Gulf War research center at University of Texas Southwestern is focused on identifying specific biological processes that underlie veterans’ symptoms
- Despite promising developments, overall funding for Gulf War research has declined substantially since 2001
Gulf War Illness and the Health of Gulf War Veterans: Scientific Findings and Recommendations

- Key Findings of the Report
  - Impact of Gulf War Illness, other Gulf War-related health issues
  - What Caused Gulf War Illness?
  - Biological Characteristics of Gulf War Illness
  - Federal Research on the Health of Gulf War Veterans

- Recommendations

Gulf War Illness and the Health of Gulf War Veterans

Recommendations

- Specific research recommendations on each scientific topic
- Funding recommendations
- Programmatic recommendations
Gulf War Illness and the Health of Gulf War Veterans

- Programmatic Recommendations
  - That VA commission the Institute of Medicine to redo the *Gulf War and Health* series of reports, to adhere to requirements set forth by Congress.
  - *The revised approach should include the full range of available scientific research relevant to Gulf War illness and other health problems, and effects of Gulf War exposures.*

- Funding Recommendations
  - *Annual allocation of no less than $60 million for federal Gulf War research ($40 million to DOD, $20 million to VA)*
Gulf War Illness and the Health of Gulf War Veterans

- Scientific Recommendations; Highest priority:

Research to identify treatments that improve the health of veterans with Gulf War illness

The extensive body of scientific evidence now available leaves no doubt that Gulf War illness is real, that it is the result of neurotoxic exposures during the war, and that few veterans have recovered or substantially improved with time.
Veterans of the 1991 Gulf War had the distinction of serving their country in a military operation that was a tremendous success, achieved in short order.

But many also had the misfortune of developing lasting health problems—problems that have for too long been denied or trivialized.

Addressing the serious and persistent health problems affecting Gulf War veterans as a result of their military service remains a national obligation.

This obligations is made more urgent by the length of time veterans have waited for answers and assistance.
Thank you