

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

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**Research Advisory Committee on Gulf War Veterans' Illnesses
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**Gulf War Illness and the Health of Gulf War Veterans:
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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

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

- 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:
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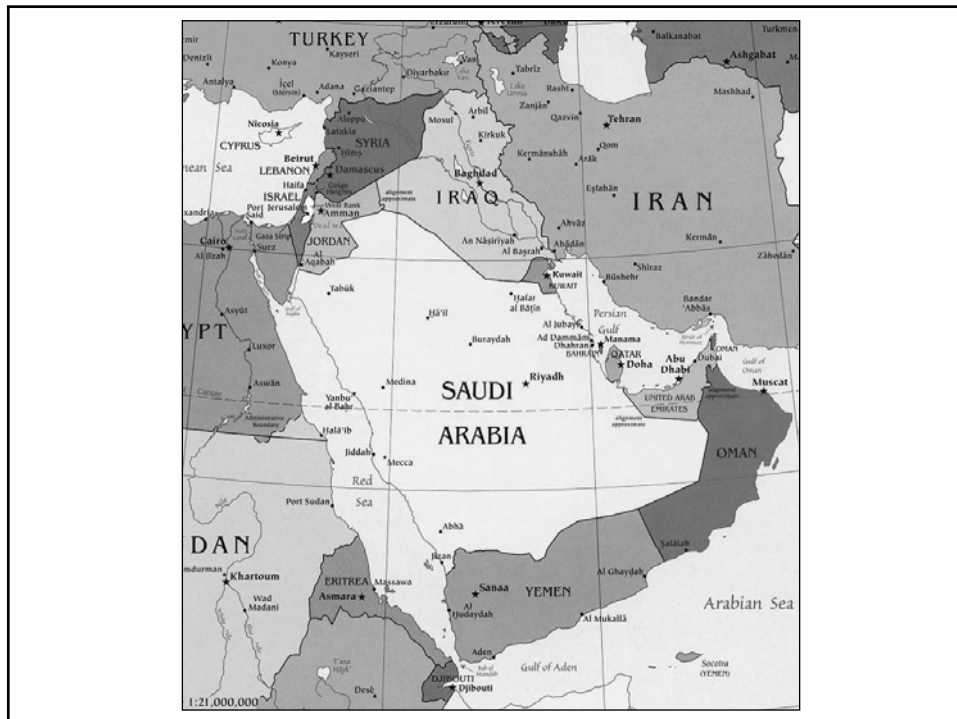
- **Background: The 1990-1991 Gulf War and Gulf War Illness**
- **Key Findings of the Report**
 - **Impact, Characteristics of Gulf War Illness**
 - **What Caused Gulf War Illness?**
 - **Biological Characteristics of Gulf War Illness**
 - **Other Gulf War-related Health Issues**
 - **Federal Research on the Health of Gulf War Veterans**
 - **Recommendations**

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

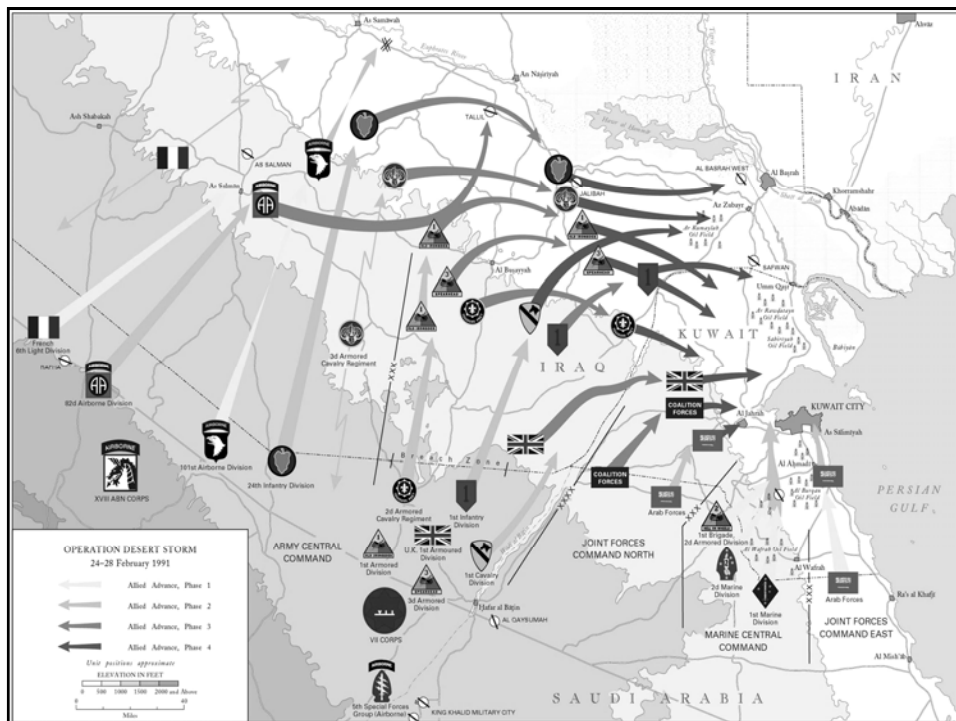


1990-1991 Gulf War: Operations Desert Shield/Desert Storm



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 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

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

- **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)

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

Veterans Studied	Number of Gulf War Veterans Assessed	Year(s) of Assessment	Case Definition Used	Prevalence in Nondeployed Veterans	Prevalence in Gulf War veterans	Excess Illness in Gulf War Veterans
Air Force veterans ⁴⁶⁴	1,155	1995	CMI	15%	45%	30%
New England Army veterans ¹²³⁸	180	1994-1996	CMI (modified)	33%	65%	32%
U.K. male veterans ¹⁶³⁸	4,428	1998	CMI (modified)	36%	62%	26%
U.K. female veterans ¹⁶³⁹	226	1998	CMI (modified)	35%	64%	29%
Kansas veterans ¹⁴²⁶	1,548	1998	GWV (KS) CMI	8% 20%	34% 47%	26% 27%
U.S. national study, Phase III ¹⁴²	1,035	1999-2001	CMI (modified)	16%	29%	13%
U.S. national study, longitudinal sample ^{745,748}	5,767	2005	Multisymptom illness*	10%	35%	25%

Abbreviations: CMI = chronic multisymptom illness as defined by Fukuda,⁴⁶⁴ Gulf War illness = Gulf War illness, KS = Kansas case definition¹⁴²⁶
 Notes: *Multisymptom illness defined as multiple types of symptoms occurring together, not explained by medical or psychiatric diagnoses

**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

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

- **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 ?**

What Caused Gulf War Illness? 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
 - Serving in combat
 - Seeing buddy killed, other casualties
 - Being shot at
 - Close to exploding SCUD
 - Family problems back home
- Chemical weapons
- Oil well fires
- Depleted uranium
- Insecticides/repellants
- Pyridostigmine bromide pills
- Vaccines
- Infectious diseases
- Tent heaters
- Particulates
- Fuel exposures
- Solvents, CARC paint



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



Diverse Gulf War-related experiences and exposures of potential concern

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

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

Study	Sample	Combat Association Evaluated	Unadjusted Association	Association Adjusted For Other Exposures
Cherry ²⁴¹ 2001	7,971 U.K. Gulf War vets	Correlation of combat with seven symptom domains, overall symptom severity, peripheral neuropathy, widespread pain	Not reported	None significant
Gray ²²⁷ 2002	3,831 Navy Seabees	Combat as a risk factor for study-defined Gulf War illness	OR = 2.6*	Not significant
Nisenbaum ¹²⁴ 2000	1,002 Air Force vets	Combat duty in relation to severe or mild-moderate CMI	Not significant	Not significant
		Coming under attack in relation to severe or mild-moderate CMI	OR (severe) = 2.4* OR (mild-moderate) = 1.1	OR (severe) = 1.2 OR (mild-moderate) = 0.7

Abbreviations: OR = odds ratio, CMI = chronic multisymptom illness⁶⁴

* = 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

Study	Sample	PTSD Measure	PTSD Prevalence	
			Gulf War Veterans	Nondeployed Veterans
<u>Population-based samples</u>				
Blanchard ¹⁴²	2,189 U.S. vets	CIDI	3.3 %	2.0 %
Toomey ¹⁵⁴⁹		CAPS	6.2 %	1.1 %
Ikin ⁹⁷⁴	2,758 Australian vets	CIDI	5.1 %	1.7 %
Wolfe ¹⁹⁰³	252 U.S. Army vets	CAPS, SCID	5.4, 7.2 %	0 %
<u>Gulf War Registries</u>				
Engel ⁴⁰⁹	21,232 U.S. vets in CCEP	Clinical diagnosis	5.6 %	
VA ¹⁹⁵¹	70,385 U.S. vets in VA Registry	Clinical diagnosis	3.8 %	
Lee ⁸⁷⁹	3,233 in U.K. MAP	Clinical diagnosis	12.0 %	

Abbreviations: CCEP = DOD 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 sign. risk factor for Gulf War illness
 - ✓ Multiple studies have identified PB dose-response effects
 - ✓ PB side effects during deployment sign. associated with increased rate of GWI
 - ✓ 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 same mechanism as pesticides, nerve agents

Review of Evidence on the Causes of Gulf War Illness

- **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 sign. 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 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

Table 2. Gulf War Illness in Relation to Experiences and Exposures During the 1990-1991 Gulf War: Summary of Evidence from Studies of Gulf War Veterans

	Epidemiologic Studies of Gulf War Veterans: Association of Deployment Exposures With Multisymptom Illness					Clinical Evaluations of Gulf War Veterans: Association of Deployment Exposures with Measured Clinical Outcomes
	Preliminary Analyses* (no controls for other exposures)		Adjusted Analyses* (controlling for effects of other exposures)			
	GWV populations in which association was assessed ^a	GWV populations in which association was sign. ^b	GWV populations in which association was assessed ^a	GWV populations in which association was sign. ^b	Dose-response effect identified?	
Pyridostigmine bromide	10	9	6	6	Yes	associated with sign. neurocognitive and HPA differences in Gulf War veterans
Pesticides	10	10	6	5	Yes	associated with sign. neurocognitive and HPA differences in Gulf War veterans
Psychological stressors	14	13	7	1		
Chemical weapons	16	13	5	3		associated with sign. neuroimaging and neurocognitive differences in Gulf War veterans
Oil well fires	9	8	4	2	Yes	
Number of vaccines	2	2	1	1	Yes	
Anthrax vaccine	5	5	2	1		
Tent heater exhaust	5	4	2	1		
Sand/particulates	3	3	3	1		
Depleted uranium	5	3	1	0		
Solvents	4	4	1	0		
Fuel exposures	5	4	2	0		
CARC paint	3	2	0	0		

Abbreviations: GWV = Gulf War veterans, sign. = statistically significant, HPA = hypothalamic-pituitary-adrenal axis, CARC = chemical agent resistant coating
 Notes: *Detailed results for all exposure variables are provided in Appendix A. Preliminary analyses refer to methods that did not adjust for effects of other exposures during deployment.

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

- Psychological stress Evidence consistently indicates no association

- 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

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

Study	Group Studied	Method(s)	Key Findings
Newmark ¹⁰³ 1995	65 active duty GWV evaluated in the CCEP	EEG	No EEG abnormalities identified
Haley ⁹³ 1997	23 GWV with Haley Syndromes, 10 well GWV, 10 nondeployed controls	MRI, SPECT	No MRI differences between cases and controls. Similar proportion of cases and controls had foci of T2 signal intensity in subcortical white matter (26-30%). No SPECT abnormalities identified.
Arnato ⁹⁸ 1997	20 GWV referred for neurological evaluation	EEG, CT	No abnormalities on EEG, CT scans of the head.
Haley ⁹³ 2000	22 Navy Reserve GWV with Haley syndromes, 2 nd sample of 6 GWV with Haley Syndrome 2, 18 veteran controls (9 GWV, 9 nondeployed)	Proton MRS	NAA/creatine ratio sign. lower in symptomatic GWV than controls: Syndrome 1 in basal ganglia, Syndrome 3 in brainstem, and Syndrome 2 in basal ganglia (14%) and brainstem (26%). Choline/creatine ratio sign. lower in basal ganglia of Syndrome 1 GWV than in controls. Syndrome 2 findings replicated in 2 nd GWV sample.
Meyerhoff ¹⁰² 2001	11 GWV with CMI, 11 nonveteran controls	Proton MRS	NAA/creatine ratio sign. lower in right basal ganglia of ill GWV veterans compared to controls. No differences in choline/creatine ratio.
Lee ⁹⁷ 2005	33 symptomatic GWV evaluated in the UK GVMAP	EEG, CT or MRI	Results reported as "no evidence of any neurological disorder" specific measures not provided.
Meron ¹⁰² 2004	10 symptomatic GWV, 5 nonsymptomatic GWV, Vietnam veteran controls	Proton MRS	NAA/creatine ratio in hippocampus was sign. lower in symptomatic GWV than in GWV and Vietnam controls, and in younger GWV than older GWV. No difference in choline/creatine ratios.
Levine ⁹⁵ 2006	27 symptomatic GWV, 15 GWV with PTSD, 11 symptomatic nondeployed GWV, 4 nonsymptomatic GWV	EEG	GWV had no abnormalities on EEG
Spence ¹⁰² 2006	21 GWV with Haley syndromes, 17 veteran controls (9 GWV, 8 nondeployed)	SPECT	Using a modified method to control for global signal effect, Syndrome 2 GWV had sign. lower average intrasubcortical blood flow and regional emission in areas of insula and frontal cortex. Effects were not observed using standard global scaling measure.

Abbreviations: GWV = Gulf War veterans, CCEP = DOD's Comprehensive Clinical Evaluation Program, EEG = electroencephalogram, MRI = Magnetic Resonance Imaging, MRS = Magnetic Resonance Spectroscopy, CT = Computerized Tomography, GVMAP = Gulf Veterans' Medical Assessment Program (U.K. registry for GWV), NAA = N-acetyl aspartate, SPECT = Single Photon Emission Computed Tomography, CMI = chronic multisymptom illness, * sign. = statistically significant

Biological Characteristics of Gulf War Illness

Brain structure and function: Neuroimaging Studies

<i>Evaluation Method</i>	<i>Results Summary (symptomatic Gulf War veterans vs. controls)</i>
H ₁ MRS, SPECT, MRI volume assessment	Significant differences identified in 6 of 7 studies
Standard neuro exam, EEG, MRI, CT scans	No differences identified (0 of 4 studies)



Table 4. Neurocognitive Evaluation of Gulf War-Deployed Veterans Overall, Not Differentiated by Veterans' Health Status

Study	Sample	Key Findings
Goldstein ¹⁰⁶ 1996	21 GWV, 38 nonveterans	GWV had sign. lower overall test performance, as measured by global impairment index based on 14 tests. No sign. differences on individual tests. Adjustment for psychological covariates reduced or eliminated group differences.
Axelrod ⁹ 1997	44 male GWV from Army Guard unit	Compared to normative values, GWV had sign. deficits on measures of motor speed and executive functioning.
Silantea ¹⁰² 1997	49 GWV from a single Army reserve military police unit	Neuropsych test performance sign. corr. with emotional dysfunction.
White ¹⁰⁰ 2001	193 GWV, 47 Germany deployed veterans	GWV scored sign. worse on tests of attention and executive functioning and mood states. Only mood functioning scores differed sign. after controlling for multiple comparisons and psychological diagnoses.
Linden/Heeres ¹⁰³ 2003		In GWV, sign. corr. between PTSD severity and poorer performance on tests of intellectual ability, sustained attention, motor speed and coordination, verbal learning, and mood. PTSD-related effects differed in veterans who did/did not report exposure to chemical agents.
Linden/Proctor ¹⁰¹ 2003		Sign. more neuropsych symptoms reported by GWV than Germany deployed veterans. GWV neuropsych symptoms not sign. associated with performance deficits but were correlated with mood measures.
Linden/White ¹⁰² 2003		In subset of 58 GWV and 19 Germany-deployed veterans tested for motivation and effort, most had perfect or near-perfect scores; similar subset of GWV and Germany deployed scored suboptimally.
David ⁹⁵ 2002	207 British GWV, 78 nondeployed era veterans	GWV had sign. worse performance on tests of verbal and intellectual performance, motor speed, and dexterity. Differences were reduced or eliminated with adjustments for depression, multiple comparisons.
Gray ¹⁰⁷ 2002	3,831 GWV Seabees, 4,933 Seabees deployed elsewhere, 3,104 nondeployed Seabees	GWV had sign. higher (worse) scores than other two groups on Cognitive Failures Questionnaire.
Vaeterling ¹⁰⁸ 2003	72 GWV, 33 nondeployed veterans	No sign. difference on neuropsych measures.
Proctor ¹⁰⁴ 2003	143 Danish GWV, 72 nondeployed veterans	No sign. differences on neuropsych tests. GWV reported sign. more mood disturbances than nondeployed veterans.
Vythilingam ¹⁰⁹ 2005	14 GWV with PTSD, 23 GWV without PTSD, 22 nondeployed veterans, 29 healthy civilians	No neuropsych differences associated with PTSD or Gulf War deployment. GWV with and without PTSD and nondeployed reservists had sign. worse scores than healthy civilians on measures of visual and verbal memory.
Berish ¹⁰⁵ 2007	301 GWV, 59 era veterans deployed elsewhere	Only 1% of GWV and 4% of era veterans had neuropsych test results judged to be noncredible by independent review.

Abbreviations: GWV = Gulf War veterans, neuropsych = neuropsychological, PTSD = posttraumatic stress disorder, sign. = statistically significant, corr. = correlated

Biological Characteristics of Gulf War Illness

Brain structure and function: Neurocognitive Studies

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



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

<i>Study</i>	<i>Group Studied</i>	<i>Autonomic Tests</i>	<i>Key Findings</i>
Davis ²¹ 2000	14 GWV with CFS or ICF, 27 GWV and nonveteran controls	NMH during 3-stage lit table testing (isoproterenol in stages 2 and 3)	Sign. more symptomatic GWV had NMH response to lit in stage 1 and overall. Symptomatic GWV had sign. greater systolic BP, HR, and change in HR with stage 1 lit.
Peckerman ^{184,185} 2000, 2003	51-55 GWV with CFS or ICF (16 with PTSD), 42-47 GWV controls	BP responses to speech and arithmetic stress tests, cold pressor test, BP change between supine and standing positions	Symptomatic GWV had sign. less BP response to cognitive stressors, responses correlated with symptom severity and functional impairment. BP differences were most pronounced in symptomatic GWV with PTSD. No differences on cold pressor test.
Shariel ²⁰⁷ 2002	39 symptomatic GWV, 18 GWV controls	Valsalva ratio, standing ratio, sympathetic skin response	Findings reported as "no real differences" on any tests (statistical results not provided).
Fieder ⁴³ 2004	12 GWV with CFS, 19 GWV controls	BP and HRV response to diesel vapor exposure	Symptomatic GWV had sign. increased systolic BP and respiratory variability response to diesel vapors. They also had blunted reactivity to (less increase in BP, HRV) and recovery from behavioral tasks in the presence of diesel exposure, but not in the absence of exposure.
Stein ¹⁸¹ 2004	11 GWV with CMI (6 male/5 female), 26 FM patients, 36 controls	24 hour electrocardiogram	GWV had sign. lower 24-hour short term high frequency HRV than controls. Males and females differed on multiple HRV measures over the 24 hour period. Overall, female GWV and FM patients had sign. less HRV than controls and male patients.
Haley ²⁶⁸ 2004	21 GWV with Haley syndromes, 17 veteran controls	24 hour electrocardiogram and BP, Valsalva ratio, tests of sympathetic function (static sweat imprint, sympathetic skin response)	Symptomatic veterans had sign. less nighttime increase in HRV high frequency power and less decrease in nighttime HR than healthy controls. No differences on measures of circadian BP, Valsalva ratio, sympathetic function tests.
Lucas ²⁰⁷ 2005	49 GWV with CMI, 44 GWV, 45 nondeployed veteran controls	BP, HR, respiratory rate, end-tidal CO ₂ , symptoms, and NMH in relation to 2 stage lit test (isoproterenol in stage 2)	Veterans with CMI had sign. more and faster onset of symptoms during lit than controls. Symptomatic GWV had nonsign. higher rate of NMH, sign. higher respiratory rate, and sign. lower tidal CO ₂ with stage 1 lit.

Abbreviations: GWV = Gulf War veterans, CFS = chronic fatigue syndrome, ICF = idiopathic chronic fatigue, NMH = neurally mediated hypertension, PTSD = posttraumatic stress disorder, FM = fibromyalgia, CMI = chronic multisymptom illness, ^{HR} BP = blood pressure, HR = heart rate, HRV = heart rate variability, sign. = statistically significant

Biological Characteristics of Gulf War Illness

Neurological function: Autonomic Nervous System (ANS) Function

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



Table 8. Evaluation of PON1 Genotype and Enzyme Activity in Gulf War Veterans

<i>Study</i>	<i>Group Studied</i>	<i>Parameter/Assay</i>	<i>Key Findings</i>
Hailey ¹⁹⁹¹	25 Navy Seabees with Haley Syndromes, 10 well GWV controls, 10 nondeployed era controls	PON1 genotype (positions 192 and 55), Enzyme activity in paraoxon, phenyl acetate (arylesterase), calculated Q,R-specific arylesterase activity	GWV with Haley syndromes sign. more likely to have PON1 R allele than controls. No sign. differences in L,M alleles. Mean PON1 activity nonsign. higher in cases, mean arylesterase activity nonsign lower in cases, type Q arylesterase activity sign. lower in cases; low Q arylesterase activity also sign. associated with having more severe side effects from PB during deployment.
Mackness ²⁰⁰⁷	152 GWV with self-reported GWI, 152 nonveteran controls	PON1 genotype (positions 192 and 55), serum PON1 concentration, enzyme activity in paraoxon and diazoxon	GWV with GWI had sign. lower PON1 concentration and activity in paraoxon than controls (activity < 50% of controls), overall and within genotype. No differences in Q,R gene frequencies or L,M frequencies in cases vs. controls. No differences in PON1 activity in diazoxon.
Hotopf ²⁰⁰³	115 "ill" GWV, 95 "well" GWV controls, 137 ill nondeployed GW era and Bosnia veterans	PON1 genotype (positions 192 and 55), enzyme activity in paraoxon	Sign. lower proportion of ill than well GWV had LM genotype (position 55). Overall, Gulf-deployed had sign. lower PON1 activity than non-PGW veterans. No sign. PON1 activity difference between ill and well GWV.
Concato ²⁰⁰⁷	140 male GWV with CMI, 125 male GWV controls, 80 nondeployed era veterans (29 with CMI)	PON1 activity (substrate not specified)	No sign. difference in adjusted mean difference of PON1 activity between cases and controls, or in deployed vs. nondeployed veterans.

Abbreviations: PON1 = paraoxonase, GWV = Gulf War veteran, GWI = Gulf War illness, CMI = chronic multisymptom illness,¹⁹¹ PB = pyridostigmine bromide, sign. = statistically significant

Biological Characteristics of Gulf War Illness	
Vulnerability to Neurotoxicants	
<i>Evaluation</i>	<i>Results Summary</i>
PON1 enzyme activity (neutralizes effects of neurotoxicants)	Significant differences associated with Gulf War illness or Gulf War service, overall, in 5 of 6 studies

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Biological Characteristics of Gulf War Illness	
Neuroendocrine function: Hypothalamic-Pituitary Adrenal (HPA) Measures	
<i>Evaluation</i>	<i>Results Summary</i>
HPA measures on GW veterans vs. nondeployed veterans	Unique profile of HPA differences on multiple HPA measures in response to adrenal challenge; sign. difference on 24-hour cortisol, ACTH
	HPA measures sign. associated with veterans use of PB, pesticides during the war
Resting cortisol, ACTH	No differences
HPA measures in relation to PTSD, combat stress	No differences

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Biological Characteristics of Gulf War Illness	
Immune function	
<i>Evaluation</i>	<i>Results Summary</i>
Circulating levels of inflammatory cytokines	Sign. increases in IFN-gamma, IL-4, IL-10 in symptomatic GW veterans in 2 of 2 studies
NK cells	Sign. reduced NK cell number and/or activity in symptomatic veterans in 3 of 4 studies
Immune competence in infection response	No differences in 4 of 4 studies
ANA, ESR	No differences in 3 of 3 studies

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- | Biological Characteristics of Gulf War Illness:
Diverse differences, most prominently relate to neurological function | |
|---|--|
| <ul style="list-style-type: none">▪ Brain structure and function▪ Autonomic nervous system function▪ Neuroendocrine (hypothalamic-pituitary-adrenal) measures▪ Measures indicative of vulnerability to neurotoxicants▪ Immune function | |
- ☆☆☆ **RAC-GWVI**
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**Gulf War Illness and the Health of Gulf War Veterans:
Scientific Findings and Recommendations**

**Other
Gulf War Health Issues**

Other Gulf War-related health issues of importance

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.

Gulf War Illness and the Health of Gulf War Veterans

- 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*



RAC-GWVI
Research Advisory Committee on Gulf War Veterans' Illnesses

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.



