Is Gulf War Illness "Real"? The Jury Is Still Out

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This author proposes that conclusions of the Research Advisory Committee on Gulf War Veterans' Illnesses are premature because the evidence on which they are based is weak.

In November 2008, after finishing its review of the research literature concerning the health of veterans of the first Gulf War, the congressionally mandated Research Advisory Committee on Gulf War Veterans' Illnesses concluded: "The extensive body of scientific research now available consistently indicates that Gulf War illness is real, that it is the result of neurotoxic exposures during Gulf War deployment…."[1] The committee further stated that this illness, which it found afflicts a quarter of the service members deployed in support of Operation Desert Storm, "typically includes persistent memory and concentration problems, chronic headaches, widespread pain, gastrointestinal problems, and other chronic abnormalities not explained by well-established diagnoses…few veterans have recovered over time."

These statements, if true, suggest a national health emergency. In addition, as the definitive statement on Gulf War illness (GWI), the effects of the committee's conclusions may have a profound effect on U.S. Government policy, such as implementation of preventive measures and determining eligibility for disability compensation. Given the committee's government pedigree, the public and even the medical community may well accept that the committee's assessment is valid and its conclusions certain.[2] But in light of the significant ramifications of the findings, 2 conditions should be met before accepting these conclusions: (1) The evidence must solidly link consistent, objective symptomatic findings to GWI and (2) there should be no plausible alternative explanations. A review of the evidence suggests that the committee's conclusions do not meet either of these criteria, at least with regard to neurocognitive data, memory in particular.

Indeed, it appears that the committee's evidence linking GWI and memory impairment, a frequently cited symptom of the illness, is weak, and that another condition, functional somatic syndrome, could explain the symptoms associated with GWI. Based on a review of the supporting literature, I believe it is premature to state with authority that GWI is "real" (meaning that it is a distinct clinical entity), includes memory problems, and is linked to chemical exposure. Here, I present the data on which I base my argument and provide recommendations for ongoing and future research.

LINK BETWEEN GWI AND MEMORY PROBLEMS

The committee grouped the neurocognitive studies on which it based its conclusions into 3 categories: studies in Gulf War veterans overall, studies in symptomatic Gulf War veterans, and studies on the relationship between neuropsychological variables and exposure to toxins.

Studies in Gulf War veterans overall

The committee concluded that these 13 studies identified no impairment of memory or other cognitive concerns because the scores of the ill were blended with scores of the well, attenuating the scores of the ill veterans and raising the possibility that significant findings could be obscured.[3] Whatever the reasons, these studies do not support that GWI is "real" as it pertains to memory.

Studies in symptomatic Gulf War veterans

Many investigations focused specifically on veterans who reported symptoms associated with GWI, but memory problems generally were not a significant finding (Table 1).[3–10] Four of these investigations studied 25 specific memory variables; none of the studies revealed significant differences when symptomatic Gulf War veterans were contrasted with either normative samples or controls when confounding factors were taken into account.[3–6]

In 3 related studies using a brief test involving learning a string of 9 digits over successive trials, no significant differences were found between Gulf War veterans with or without unexplained symptoms.[7–9] Nonetheless, the committee concluded that these studies showed

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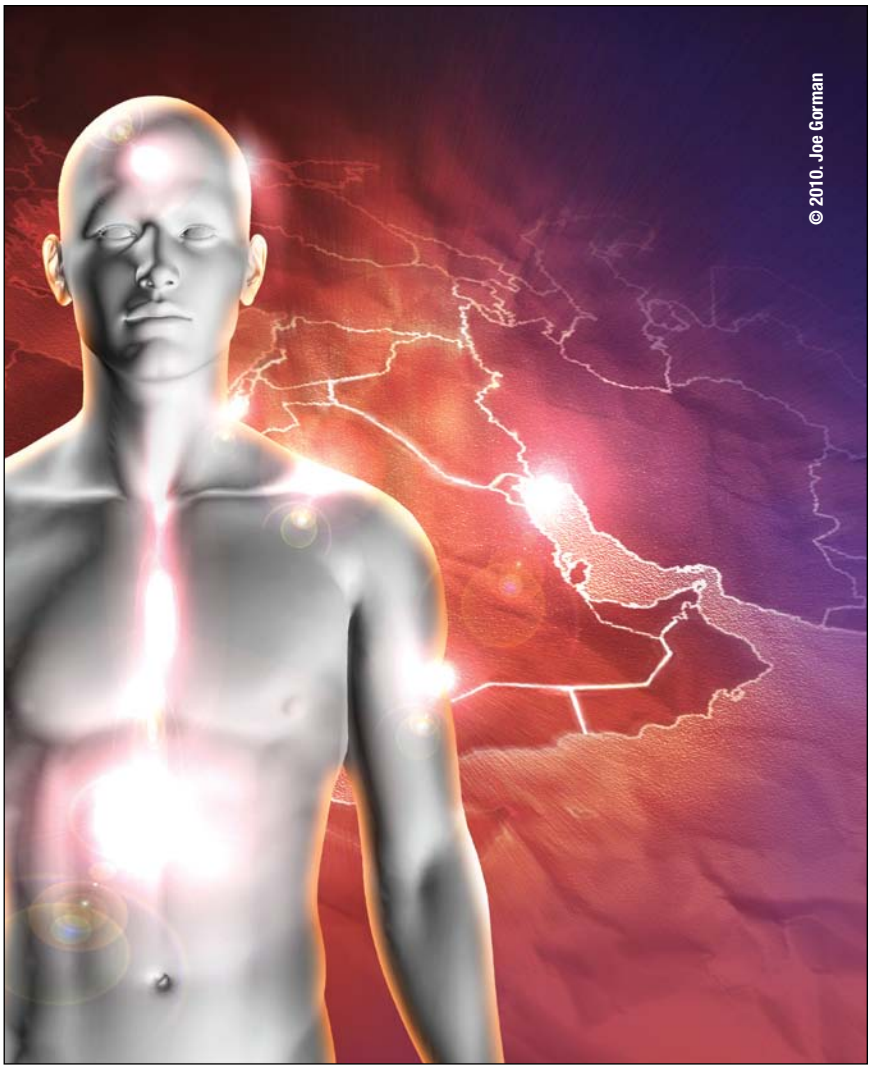
that symptomatic Gulf War veterans had significantly poorer performance on tests of "memory" than veterans without symptoms. Its rationale for this conclusion is unclear, although it may be based on results of another test that was administered in these studies, the Oregon Dual Task Procedure (ODTP). For this forced-choice test, participants first are shown brief strings of digits, then pairs of digit strings; one string is new and the other was shown previously. The respondent has to identify the previously shown digit string. This exercise is considered a test of motivation, not of memory, because the task is deceptively simple, and even individuals with clear memory impairment are expected to have near-perfect scores. That the symptomatic veterans performed significantly less well than those without symptoms, both in terms of response latency and correct answers, suggests they did not give their best effort, not that their memory was impaired.[7,8]

It also makes questionable findings that rely on these results and raises concern about why symptomatic veterans' performances would be suboptimal; possibilities include disinterest in the test and a desire to appear impaired, perhaps to obtain disability benefits, for example. Further analysis, contrasting a small subgroup of symptomatic veterans who had the slowest response speed on the ODTP with veterans with no symptoms to report, found no significant difference on the only memory test that was administered, symbol digit learning.

The committee also cited a study by Bunegin and colleagues as revealing that veterans with symptoms had "poorer performance on tasks of memory…." than veterans without symptoms.[10] The study authors administered 9 brief computerized tests to 8 symptomatic veterans and 8 controls; the only memory test used involved "pattern memory." No difference was noted between the groups when this test was administered during 3 air/breathing treatment conditions; when data were pooled, however, pattern memory was significantly poorer for the symptomatic veterans. On the other hand, the study does not account for the large variable-to-participant ratio, participant effort, or that the symptomatic veterans reported significantly greater psychiatric difficulties. These findings, therefore, are inconclusive.



Studies on the relationship between neuropsychological variables and exposure to toxins

The committee cited 6 studies of 5 memory tests comprising about 44 memory variables (Table 2).[11–16] Only 2 of these studies suggested a relationship between toxin exposure and memory.[13,14] Those investigations, which compared findings in Gulf War veterans and other veterans (controls), examined the relationship between self-reported toxin exposure and portions of the Wechsler Memory Scale (WMS) and California Verbal Learning Test (CVLT). Of the 26

Table 1. Memory test results in symptomatic veterans

Reference	Memory tests administered/variables	Memory findings
David, Farrin, Hull, et al[3]	• Wechsler Memory Scale–Revised: logical memory immediate and delayed; verbal paired associates immediate and delayed • Camden Recognition Memory Tests: faces and words	Not significant
Lange, Tiersky, DeLuca, et al[4]	• California Verbal Learning Test: short and long delay free recall • Rey-Osterreith Complex Figure: immediate and delayed free recall	Not significant
Axelrod, Milner[5]	• Rey Auditory Verbal Learning Test: trial 1; trial 5; trials 1–5; retention; 30-min delay; recognition hits; intrusion words • Wechsler Memory Scale – Revised: prorated general memory and delayed recall indices	Not significant
Hom, Haley, Kurt[6]	• Wechsler Memory Scale – Russell Revision: verbal immediate and delayed recall; figural immediate and delayed recall • Tactual performance tests: memory and localization	Not significant
Anger, Storzbach, Binder, et al[7]	Serial digit learning	Not significant
Storzbach, Campbell, Binder, et al[8]	Serial digit learning	Not significant
Storzbach, Rohlman, Anger, et al[9]	Serial digit learning	Not significant
Bunegin, Mitzel, Miller, et al[10]	Pattern memory	Not significant except with pooled data across 3 breathing test conditions with symptomatic (n = 8) vs asymptomatic (n = 8) Gulf War veterans

CVLT variables, exposed Gulf War veterans performed significantly less well with regard to only the number of perseverative responses (that is, gave the same answer more than once) on delayed cued recall in 1 study and on Trial 2 (of 5 trials) and short delayed recall on the second study. The exposed Gulf War veterans and controls did not differ significantly in perseverative responses for other memory variables or in other recall ("memory"). In addition, exposed Gulf War veterans performed less well than controls for 1 of 10 WMS variables in each study, delayed visual reproductions; differences in all other WMS variables were not significant. Given that significant differences between the 2 groups were found for only 4 of a large number of memory variables included in these studies, the observed differences likely represent incidental findings.

To summarize, studies of memory in Gulf War veterans have included a large number of tests, many with numerous variables. Most have not found a relationship between memory and GWI. Few findings have had statistical significance, and even these findings are isolated, inconsistent across studies, and likely not of clinical relevance. Therefore, the first criterion for accepting that GWI is "real" and includes memory deficits—that the evidence solidly links consistent, objective symptomatic findings to GWI—has not been met.

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Table 2. Memory test results in neurotoxin-exposed veterans

Reference	Memory tests administered/variables	Memory findings
Sillanpaa, Agar, Milner, et al[11]	RAVLT–delayed recall	Not significant
Vasterling, Brailey, Tomlin, et al[12]	• RAVLT: total trials 1–5; savings ratio • Continuous Visual Memory Test: total correct learning and delay	Not significant
White, Proctor, Heeren, et al[13]	• WMS–Revised Paired Associate Learning: immediate and delayed recall • CVLT: recall for each of trials 1–5; interference list recall; short and long delay cued and uncued recall; recognition • WMS Visual Reproductions: immediate, delay, copy	• Oil fire exposure: not significant • Pyridostigmine bromide pills exposure: not significant • Chemical warfare exposure: significant only for WMS visual reproductions delayed recall and CVLT trial #2 and short delayed recall
Lindem, Heeren, White, et al[14]	• CVLT: total correct, clusters, perseveration, and intrusions for each of trials 1–5, Tuesday list, short delay recall, short delay cued recall, long delay recall, and long delay cued recall; number correct recognition • WMS–Revised Verbal Paired Associate: easy and hard items for both immediate and delayed recall; total recall immediate and delayed • WMS Visual Reproductions: immediate and delayed recall, recognition, copy	Self-reported exposure to chemical-biologic warfare agents related only to CVLT delayed cued recall perseverations and WMS delayed visual reproductions total
Proctor, Heaton, Heeren, et al[15]	• WMS–Revised Verbal Paired Associate Learning: difficult items and delayed recall • WMS Visual Reproduction: immediate and delayed recall • CVLT: short and long delay recall	Not significant
Sullivan, Krengel, Proctor, et al[16]	Selected measures: • WMS–Revised Verbal Paired Associate Learning: immediate and delayed easy and difficult recall • WMS Visual Reproductions: immediate and delayed recall • CVLT: trials 1–5 correct; short and long delay free recall; short and long cued recall; recognition • Rey-Osterreith Complex Figure Test: immediate and delay	Toxin vs nontoxin exposure: not significant

CVLT = California Verbal Learning Test; RAVLT = Rey Auditory Verbal Learning Test; WMS = Weschler Memory Scale.

Other study-related factors also throw doubt on the committee's conclusions about GWI (see "Evaluating Gulf War Illness Studies" on page 18).

AN ALTERNATIVE EXPLANATION FOR GWI SYMPTOMS

So we have a condition that has no identifiable cause, no accepted diagnostic nomenclature, and no validated diagnostic assessment methods; it is characterized by nonspecific symptoms, including those that are

Table 3. Recommendations for ongoing research conducted by the Research Advisory Committee on Gulf War Veterans' Illnesses

- Restrict membership of the committee to individuals with no potential conflict of interest in the committee's conclusions. It would be challenging for current committee membership, including 2 reporting to have GWI and 1 who is Deputy Director for Claims Services for the American Legion, to remain objective. Also, the committee should include clusters of researchers who can focus on specific areas—for example, a select group of neuropsychology experts who review the literature and function as 1 voice on the committee—to allow for diverse perspectives and cross-checking of opinions. To avoid unintended interpretive bias, the committee should also include scholars who are not actively researching GWI but who are experts in their respective fields.
- Recruit independent scholars to examine specific aspects of the committee's findings based on the scholars' particular areas of expertise.
- Conduct focused research on cognitive functioning by testing specific hypotheses regarding particular skills and test findings. This research should not rely on the shotgun methods that were useful in the early stages of GWI research for flushing out variables.
- Use statistical methods that include accounting for variable- to- sample ratios.
- Distribute research grants among researchers unaffiliated with each other to allow a diverse range of opinions and perspectives.
- Apply research methods used with functional somatic syndrome. For example, assess subtle psychosocial and work environment variables that may play an etiological role in GWI.
- Use objective research methods rather than self-report, to the extent possible.
- Conduct studies that address the functional impact of GWI.

GWI = Gulf War illness.

cognitive, psychological, and neurologic: fatigue; headache; weakness; muscle aches; joint pain; problems with memory, attention, and concentration; gastrointestinal symptoms; anxiety; depression; and irritability. This condition affects a proportion of the normal population, involves a large number of individuals working in close proximity, is associated with an environmental event, and is refractory to treatment.[17–22] Is the condition GWI? Perhaps, but this clinical picture also fits another set of conditions—functional somatic syndromes.

Functional somatic syndromes include multiple chemical sensitivity, adverse effects of silicone breast implants, fibromyalgia, and chronic fatigue syndrome.[17,23] Similar vague medical conditions have been related to the work environment: sick building syndrome (SBS), building-related illnesses, neurotoxic disorders, and mass psychogenic illness.[22] While all these conditions are different in subtle ways, for example some are insidious while others are characterized by rapid onset, their similarities are striking and suggest they are all the same illness, one that can be described as a variant of somatoform disorder.[24]

Psychological variables are thought to play a strong, if not primary, role in the etiology of functional somatic syndromes. It is considered unlikely that these conditions are caused by traditionally defined neurologic disease.[23] Instead, a combination of biologic and psychological factors is thought to be at play. Environmental and personality variables also are implicated in the etiology of functional somatic syndromes. A summary of the medical literature on mass psychogenic illness noted that the following factors were associated with ill patients: work or educational environments that presented little choice but to remain; pressure to increase performance; and physical stressors—all factors that are common in Gulf War veterans.[21]

Similarly, a survey of hospital personnel in the Halifax, Canada area, some of whom worked in known sick building sites, showed that those at sick building sites who experienced great organizational stress were most likely to report that their health had been adversely affected by their place of employment.[19] Also, individual reports of poor air quality, regardless of whether the individual worked at a sick building site, was associated

Evaluating Gulf War Illness Studies

While many studies address the incidence of symptoms associated with Gulf War illness (GWI), few investigations examine the incidence of objective findings suggesting the presence of GWI. An examination of neurobehavioral deficits in Persian Gulf veterans found a potential subgroup of 13 of 101 randomly selected participants who were "slow" responders to neurobehavioral tests.[1] Although the authors noted that these veterans always could have been "slow" or simply did not put forth their best effort when tested, were it assumed that all 13 of these individuals had "real" GWI, they still constitute only about 13% of the sample. Regardless, their performance on memory testing was normal as compared with that of the other study participants. Yet, the Research Advisory Committee on Gulf War Veterans' Illnesses declared that more than a quarter of Gulf War veterans have GWI, including memory problems.[2] Of note, studies cited by the committee rarely found objective memory problems, and the few studies that did had methodologic issues, making the committee's interpretation questionable.

Additionally, studies consistently show that those who report GWI symptoms perform less well than controls on effort and validity measures. Such findings generally have been dismissed because the group means of the GWI participants on tests of effort were still within 1 standard deviation of the test norms, no participant performed below cut-off for likely invalid testing, or because those participants who performed below the invalid cut-off were deleted from study results.[1,3,4] However, poorer effort, even if not at the level strongly suggestive of intentionally performing suboptimally, has been associated with reduced performance on tests of attention, executive functioning, and memory—cognitive skills the committee links with GWI.[5] The few significant findings the committee notes, then, may be attributable, at least in part, to reduced effort.

That a large number of studies rely on self-report, which is notorious for reliability and validity problems, also is an important factor. In their 2-stage study of changes in recall of traumatic and toxic hazards among United Kingdom Gulf War veterans, Wessely and colleagues found that more exposures were reported over time and that such reports are related to current self-rated perception of health as well as media publicity.[6] Similarly, Mahan and colleagues found that in Gulf War veterans, all of whom had received the anthrax vaccine, incidence of self-

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with "role conflict, role overload and organizational stress," suggesting, the authors noted, that SBS may not be entirely dependent on environmental factors. Of interest, those who reported higher levels of organizational and union support were more likely to be at sick building sites, possibly reflecting an acceptance of the union and the employer regarding sick building as a medical condition; in other words, individuals at these sites may be made more aware of possible symptoms, be more prone to suggestion, feel freer to report their symptoms, and be more likely to pursue secondary gain issues such as disability compensation.

In another example, investigators found that individuals in a "classic sick building" (symptoms reported by chronic occupants but no objective evidence of pollutants or poor air quality) could be differentiated from controls in a non–sick building by increased "defensiveness, resentment and distrust of authority, anxiety, and confusion"; they concluded that while SBS likely is not caused exclusively by psychological factors, "it is not psychologically benign."[20] A survey of 346 individuals working in offices at 5 different buildings in England—none of which had known environmental problems—found that increased reporting of SBS symptoms was associated with low autonomy at work, work-related depression and anxiety, and negative affect, whereas job satisfaction was negatively associated with symptoms typical of SBS. The authors acknowledged that environmental causes of these results could not be ruled out, however.[18]

Given these findings, could it be that GWI is a functional somatic syndrome variant? This possibility cannot be ruled out. Certainly, the reported symptoms and certain aspects of the work environments are similar in both conditions. Whether the psychological variables, such as those associated with SBS, also are the same may be a promising area for future research.

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reported disability, utilization of health care resources, and incidence of medical conditions were higher among those who reported being exposed to the vaccine than among those who mistakenly thought they had not been exposed to the vaccine.[7] A study of neuropsychological functioning in Gulf War veterans exposed to pesticides noted that 47% of veterans who self-reported exposure to toxins reported "forgetfulness"; however, in a preliminary stage of this study, an outside research firm found that only 9% reported memory problems—more evidence of the difficulty self-reported data presents.[8]

Research suggests that the symptoms associated with GWI not only are not specific to this illness but also are common in healthy individuals from the general civilian population. In comparing a group of symptoms in patients with mild traumatic brain injury and healthy controls, Paniak and colleagues found that 33% of controls experienced fatigue and 58% headaches; 47% of controls reported word-finding problems, 46% distractibility, 35% poor concentration, 47% forgetfulness, and 47% irritability.[9] Another study of medically unexplained symptoms also noted that pain reports are high in the general population.[10] Self-reported symptoms thought to be consistent with GWI therefore are not specific or uncommon, which suggests GWI may represent, at least in part, reports of normal, everyday issues that a large percentage of the general population experiences.

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But why do so many veterans report GWI symptoms, and why is the subjective report of symptoms considerably in excess of what can be discovered through objective examination?[23] In their review of functional somatic syndromes, Barsky and Borus—who included GWI in a list of functional somatic syndromes—offer several possible explanations.[17] For one, the prevalence of functional somatic syndromes overall appears to have increased in recent years, in part because of a decrease in physicians' authority and prestige. This leads patients to disbelieve their providers' assurances that they are not seriously ill, and they instead rely on the Internet and other alternative information sources, which reinforce their fears. This situation is exacerbated by sensationalized media coverage of functional somatic syndromes. Finally, some parties have a vested self-interest in enhancing the status of functional somatic syndromes: Researchers can benefit from increased publication opportunities, grant potential, and academic promotion and tenure opportunities; antimilitary groups and individuals can use GWI as support for their views; and individuals who are declared disabled stand to reap a lifetime of substantial benefits, including disability payments and medical care.

THE BOTTOM LINE

GWI has presented research difficulties for nearly 20 years. While it is tempting to reach a definitive conclusion as to whether GWI is "real" and to identify what causes it, hasty and potentially incorrect conclusions are worse than none at all. Because current findings do not support the conclusions of the committee, I believe the committee should consider implementing some new approaches in its ongoing work, including restricting membership to individuals with no potential conflict of interest (Table 3).

In the meantime, research shows there are viable alternatives to the notion that GWI is a distinct clinical entity and is caused by chemical exposures. GWI could be a functional somatic syndrome or merely the normal everyday forgetfulness reported

by the general population. Other possibilities are that some veterans may overreport symptoms and underperform on tests because they believe they have contracted GWI; research has shown that simply reporting toxin exposure is associated with increased reporting of symptoms regardless of actual exposure.[25] Other possibilities may exist as well. But what is clear is that GWI is not the only possible explanation for Gulf War veterans' subjective and unexplained memory symptoms. ●

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