

Gulf War Syndrome is a Neurological Disease. There's No Treatment, but Physician and Claims Adjudicator Alike,
DO NO HARM

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Now, when nearly one-million veterans of the War on Terror queue for disability determinations from The Department of Veterans Affairs and new claimants continue to emerge from The Vietnam War, the Veterans Administration faces another huge challenge. That is what to date has been considered a “soft diagnosis”, like Fibromyalgia, Post-concussion Syndrome, Posttraumatic Stress Disorder or Chronic Fatigue Syndrome, where medical complaints and disability require astute clinical diagnosis and oftentimes draining compassion rarely supported by hard evidence from the lab or x-ray. An estimated 150,000 veterans deployed to the 1990–1991 Persian Gulf War returned with persistent unexplained body pain, fatigue, headache, irritable bowel, urinary problems, sexual dysfunction and intellectual deficits. Gulf War veterans were exposed to a wide variety of atmospheric pollutants that included nerve gas, either fired at them in warheads of Scud Missiles (unconfirmed) or released by US airstrikes on Iraqi chemical warfare factories (confirmed). There were also pesticides and toxins from burning oil fields, as well as inoculations unproven in human trials, but successful with animals, to prevent lethal effects of Sarin and Soman Nerve Gases.

Known for over a decade as “Gulf War Syndrome”, it has been both perplexing to physicians and debilitating for soldiers fighting in certain campaigns of Saddam Hussein’s “Mother of all Battles”. Always a curious term to use, I wondered if he meant the toxic atmosphere to which our 700,000 soldiers would be exposed could poison fathers, damaging procreativity for generations to come. Perhaps he was not that intelligent, but now there is indisputable evidence that he did just that, either directly or indirectly.

Long-term studies of Gulf War I veterans consistently show robust persistency of debilitating symptoms – not always progressive – but certainly disabling without relief from any treatment so far tried for more than a decade. Not many doctors have the patience, time and the clinical skills to work effectively with civilian patients with such soft diagnoses as Chronic Fatigue Syndrome or Fibromyalgia, whose suffering and disability cannot be objectively supported on examination, lab or x-ray exam. And, there is no consistently effective treatment known to either validate or ameliorate their suffering and debilitation. In the Department of Veterans Affairs clinics, it is even worse; these patients don't just have one or the other, but at least Chronic Fatigue Syndrome and Fibromyalgia, along with other debilitating syndromes – sexual dysfunction – and memory loss – even, possibly, birth defects. Within the VA, it is known as “Chronic Multisymptom Illness”.

According to recent research findings at Southwestern Medical College in Texas, however, principal researcher, Dr Robert Haley, has stuck it out with these frustrating patients and discovered robust neurological dysfunction - even after the Department of Veterans Affairs cut off his research funding for wasting taxpayer monies! He carried on with local funding but humbly retorts, “their illness is controversial; the US government has never acknowledged that Gulf War syndrome is a real illness, and many people still believe it's psychological”.

And Gulf War veterans with “Chronic Multisymptom Illness”, a diagnosis that won few patient and compassionate doctors in a VA system overwhelmed by many hundreds of millions of dollars' worth of long-term disability claims for Posttraumatic Stress Disorder and Traumatic Brain Injury, will experience less friction along the slide to care and long-term disability claims adjudication. To date they have been treated with everything from antibiotics to psychotherapy with no benefits; with Dr Haley's research at Southwestern and more recent Functional MRI imaging at Georgetown, we know why; Gulf War Syndrome, like Multiple Sclerosis, is not just a soft multisymptom diagnosis, but a hard, chronic and debilitating neurological diagnosis demanding a significant investment in research for effective treatments. So here is what the disabled veteran with intellectual

impairment, inability to sit due to pain and impaired with severe fatigue has to face with his claims adjudicator to get both long-term disability compensation – there is no recovery anticipated for these patients – and at least compassionate, symptomatic care.

"Gulf War Veterans with the following presumptive illnesses do not need to prove a connection between their military service in the Southwest Asia theater of military operations and these illnesses:

- Medically unexplained illnesses (popularly called "Gulf War Syndrome")
- Infectious diseases

Presumptive diseases: VA decides which Gulf War Veterans' illnesses are 'presumptive' based on medical and scientific evidence of connections between the illnesses and exposure to toxic agents, environmental or wartime hazards, or preventive medicine during military service."

I find this insurance medicine eligibility statement particularly confusing and likely defensible in claims appeals processes either way it is interpreted – i.e. “veteran is service connected for Chronic Multisymptom Illness” or “veteran has not made an adequate case for his symptoms being either physically disabling or caused by military service”.

In a recent Forbes article, a patient who was found eligible for service connected disability, is quoted in response to robust evidence of his neurological vs. psychological disability – or, “all-in-his-head or imagined”, aka “functional” complaints. “Ronald Brown, 45, has encountered this attitude from some VA doctors, though he speaks highly of his current physician. Brown, who is considered 100 percent disabled by VA, has been diagnosed with numerous maladies – chronic fatigue syndrome, respiratory disease, fibromyalgia, migraines, sinusitis, irritable bowel syndrome and post-traumatic stress disorder – in the years since serving as an Army soldier in

Desert Shield/Desert Storm from August 1990 through April 1991. 'I was hoping (the Georgetown University research study he was in) would provide answers to me about exactly what was going on,' he said. 'I was hoping it would provide information to other sick veterans from the Gulf and maybe give them some peace of mind.' That relief can't come soon enough for Brown, who takes 24 medications and five inhalers to control his symptoms. 'On the bad days, it's complete misery,' he said. 'I'm not able to play with my daughter, I can't run around. I feel like I've been robbed of what I should be able to do.' Brown suspects that his disease may be related to exposure to chemical warfare agents in Khamisiyah, Iraq in March 1991, an incident that the Department of Defense has documented. Brown says he suddenly experienced profuse sweating, headaches and nausea during this period. When he returned home the next month, he was unable to perform well on physical endurance tests, and began noticing symptoms that would plague him for the next two decades.'" "A New Step in Solving the Mystery of Gulf War Illness" Rebecca Ruiz, Forbes, 6/14/2013

What has the latest Neurological research on Gulf War Syndrome shown?

"We've shown there are differences in MRI findings between high- and low-symptom Gulf War veterans. In recent times, the Institute of Medicine and other groups have come out more or less attributing these symptoms to psychiatric conditions and implying there was no physical basis for them, but we've shown this is not the case," Roberta White, PhD and Dr Ronald Killany of Boston University compared MRI imaging of high and low symptom groups of Gulf War Syndrome patients. They found measurable differences within deep brain structures whose functions include filtration and discrimination of internal stimuli, such as emotion, and external, such as getting burned. These included the deep brain and ontogenically more primal Cingulate Gyrus and Caudate Nuclei necessary for primates' red tooth and claw survival. These structural differences not only were evidence of brain damage in Gulf War Syndrome, but they correlated with even more significant gradients in Neuropsychological testing of learning and memory. Another significant finding was that brain damage found correlated with dose

of exposure to pesticides used to rid troops of sand fleas and other desert insects, as well as exposure to the chemical-warfare agents sarin and cyclosarin, caused when allied troops blew up a munitions storage facility in Khamisiyah, Iraq, in March 1991. "It is pretty clear that something's happening to the vets' [central nervous system] CNS function and brain structure... This is an "important first step for Gulf War veterans as well as the scientific community in validating the fact that so-called 'soft' neurological conditions can have a pathological basis.". "Structural Changes Found in Brains of Symptomatic Gulf War Veterans", Caroline Cassels. , Medscape Medical News, May 1, 2007.

More recently, Dr Robert Haley of the Clinical and Translational Research Center, University of Texas Southwestern Medical Center, Dallas, found additional evidence of Central Nervous System damage and resultant neurotransmission dysfunction in Gulf War Syndrome patients by conceptualizing the whole, rather than the parts. His patient population presented an inchoate constellation of symptoms that led him to move upstream from symptom to its regulation within the central nervous system. He thus arrived at the hypothesis that Gulf War Syndrome is, like Alzheimer's Disease, an abnormality of neurotransmission of the brain chemical, acetylcholine, both the target of treatment for memory loss in dementia, where there is a drought for this neurochemical, and chemical warfare agents such as Sarin gas, that cause an equally debilitating flood of it. "Now we need to turn our attention to looking at treatments that neurologists and internists and other doctors can provide for conditions that involve abnormalities in the cholinergic parts of the nervous system." "Gulf War Illness Linked to Cholinergic Abnormalities Medscape Medical News", Medscape News for Neurology, Pauline Anderson, Nov 26, 2012

Dr Haley focused on studying differentials and commonalities in autonomic nervous system function – that nervous system out of our voluntary control and responsible for regulating intestinal motility, bladder and sexual function, respiration, sleep-wake cycle and heartbeat. He selected 97 well-diagnosed cases of Gulf War

Syndrome and compared them to control veterans, some of whom were deployed in Gulf War I, but free of symptoms. He identified three distinct groups of highly salient symptomatology within this cohort of patients. The first mainly had trouble thinking, concentrating and remembering; their mood was also depressed. The second group suffered from confusion and poor coordination and balance problems. The third group had disabling pain without identifiable causation like arthritis. There were consistent pain complaints among this group of soldiers, describing constant pain between their shoulders and down their arms and thighs that prevented their driving in a car. Nothing relieves the pain in these veterans.

Haley used objective tests to measure the function of the autonomic nervous system in both the Gulf War syndrome patients and the asymptomatic control group and found significant differences with powerful evidence of toxic nerve damage to the Central Nervous System. These tests included the following: Validated domain scales from the Autonomic Symptom Profile questionnaire, the Composite Autonomic Severity Score, and high-frequency heart rate variability from a 24-hour electrocardiogram.

More specifically, he found that response to his testing correlated with actual length of the autonomic nerve fibers responsible for the function tested; these are the nerve fibers operating outside of volitional control - such as conscious voluntary movement, remembering, learning, thinking, suppressing sensations of pain in order to concentrate and exertion for physical activity. They are responsible for automatically maintaining internal homeostasis within the body – i.e. sleep-wake cycle, body temperature, heartbeat, digestion, sensory recognition of external stimuli and retaining experience for memory and learning. The actual autonomic nerve fibers of patients with Gulf War Syndrome were in fact shorter than the same fibers in the control group. Veterans in groups 2 and 3 had the highest scores measuring defective firing of their autonomic nervous system nerves in response to cold, but all three had impairment. Group 2 with sleep, visual and sexual dysfunction showed statistically significant highest “Composite Autonomic Severity Scores (CASS)” but the pattern of abnormality on

the CASS was similar across all three groups. A sensitive test of cardiac health known as high-frequency heart rate variability (HF HRV) increased normally at night in the control group but not in the 3 syndrome groups; again, this central nervous system function is out of our conscious control. The Autonomic Symptom Profile scales were significantly elevated in all 3 syndrome groups – especially the antigravity response of human blood pressure and pulse. The Composite Autonomic Severity Score was also higher in the 3 syndrome groups, especially in syndrome 2, primarily due to a significant reduction in a quantitative measure indicating a peripheral nerve length–related deficit.

Dr Haley suspected that the patients in Group 2 suffered from an early and non-progressive form of Alzheimer’s Disease, in which the memory bank for recent recall is located in another deep brain structure, in fact contiguous anatomically with the Cingulate Gyrus - found reduced in size in earlier studies previously cited from Boston. He stimulated this tiny brain structure to simulate its response to Sarin nerve gas and found its physiological response abnormal. Dr Haley believes that these veterans suffered the worst damage in the Gulf War and very likely were exposed to nerve gas.

"The hypothesis was that if nerve gas damaged acetylcholine receptors in these guys' brain — and there's reason to believe that that's what nerve gas does — then their cholinergic receptors wouldn't respond normally to acetylcholine. That's what we found. Those with syndrome 1 responded normally, just like the controls, whereas those in the syndrome 2 and 3 groups didn't slow down; in fact the brain sped up indicating there's an abnormality of cholinergic receptors...We bombed big storage warehouses producing fall out clouds that drifted over our troops and rained fallout on them," said Dr. Haley. “Pauline Anderson, “Gulf War Illness Linked to Cholinergic Abnormalities”, Medscape Medical News, Neurology, Nov 26, 2012

Dr Haley believes that there are a minimum of two explanations for his findings. Twenty per cent of veterans have a weak form of the gene protecting their autonomic nervous systems from Sarin nerve gas; this gene,

PON1, controls production of an antidote to nerve gas affecting cholinergic neurotransmission in the Central Nervous System. But, as Haley says, "The cloud didn't go everywhere, but if you were exposed to the cloud and you had the weak form of the gene, you've got a huge risk of being sick with chronic neurotoxic encephalopathy" which characterizes the syndrome 2 variant of Gulf War illness, he said. He believes that veterans in Group 1 with mild impairment in memory and learning may not have been exposed to more malignant nerve gas but, rather to pesticides which were heavily used in the field of operations. "We think that syndrome 1 may be a pesticide problem and that 2 and 3 are very strongly associated with nerve gas exposure and the PON gene." Pauline Anderson, "Gulf War Illness Linked to Cholinergic Abnormalities", Medscape Medical News, Neurology, Nov 26, 2012

His next paper on the pattern of autonomic symptoms and objective test results suggesting dysfunction in both central and peripheral cholinergic functions in Gulf War Syndrome, Haley believes, includes all the evidence showing how nerve gas might cause symptoms of Gulf War illness. It should, he states, "end the discussion" on this topic. He adds that his group's objective findings "will do 2 things. One, it will give an objective basis in terms of who to put on disability and who to provide service-connected benefits to. It's also a really important clue as to how to treat this." Pauline Anderson, "Gulf War Illness Linked to Cholinergic Abnormalities", Medscape Medical News, Neurology, Nov 26, 2012

And, this is critically important, because these veterans, for the most part, have not been treated well by either physicians or VA long-term disability adjudicators. In answer to the question why it took two decades to discover a neurological basis for Gulf War Syndrome, he attributed much of the problem to the patients themselves. Symptoms of fatigue, heart rate, impotence, diarrhea and unexplained pain are hard to convey to doctors in brief clinical encounters. "Cholinergic Autonomic Dysfunction in Veterans With Gulf War Illness Confirmation in a Population-Based Sample", Robert W. Haley, MD; Elizabeth Charuvastra, RN; William E. Shell, MD; David M.

Buhner, MD; W. Wesley Marshall, MD; Melanie M. Biggs, PhD; Steve C. Hopkins, BS; Gil I. Wolfe, MD; Steven Vernino, MD, PhD, JAMA Neurol. 2013;70(2):191-200. doi:10.1001/jamaneurol.2013.596.

Most recently, Georgetown University researchers used functional MRI imaging. An fMRI, or "functional" MRI, is a scan that measures actual brain activity by detecting how blood flows through the brain. Functional MRI scanning of 31 Gulf War vets showed robust damage to fibers deep inside the brain responsible for detecting and interpreting pain sensation. They "have deteriorated compared to the control. A tiny pulse of pressure is interpreted as a painful pinch, or normal muscle fatigue from walking a flight of stairs could be interpreted as climbing to the fourteenth floor. It was shocking to us," said Rakib Rayhan, lead author of the study and a researcher at Georgetown University Medical Center. "We were just floored." And, like Haley's research, subgroups showed differences. "Each subgroup had distinct areas of damage to different parts of the brain. After exercise, the ill veterans don't get the endorphin rush that appears in healthy people. Instead, they can be physically "knocked out for days," Rayhan said. Kelly Kennedy, USA TODAY, June 14, 2013

In fact, this was serious brain damage called "atrophy" – dying or dead tissue - compared to controls without multisymptom illness, considered until recently by most physicians and insurance claims adjudicators as emotional problems. Similarly to Haley's studies, researchers at Georgetown discovered that the veterans with Gulf War Syndrome had either grossly abnormal ant-gravity response of their blood pressures when sitting up – abnormal autonomic nervous system response to gravity with abnormal spike in blood pressure – or, they had a primarily lowered threshold to pain

Then there was another striking difference between normal volunteers and patients with Gulf War Syndrome. The pathways for neurotransmission in the brains of patients following a simple challenge to subjects to

remember simple text were totally different than with normal controls. Both groups of sick veterans lit up their fMRI's with circuitous neural pathways, evidencing what is known as diabolical learning of the brain's neurocircuitry. Patients with serious mental illness, Alzheimer's Disease and Multiple Sclerosis show compensatory responses to challenges such as this also, but their fMRIs are very different; Gulf War Syndrome, more likely than not, then, is a specific diagnostic disease entity with hard evidence of its neurologically dysfunctional substrate in neurotransmission on fMRI scanning.

"I'd say it's unique to Gulf War veterans," Baraniuk said, adding that the damage may show degeneration of the nervous system. "The brain has to find other routes to get the job done. We wanted to know why does exercise make these people completely fall off a cliff," Rayhan said. "It was as if you took the crutches away – those areas of the brain don't light up after exercise." Kelly Kennedy, USA TODAY, June 14, 2013

Most disturbing in this research was the discovery of brain atrophy – or dying neurons, as in Alzheimer's Disease or other degenerative brain diseases, like Lou Gehrig's Disease – (ALS). The damage in the abnormal antigravity blood pressure responders was mainly in the brain's ontogenically primitive survival region, the brain stem and cerebellum, while the group with low pain threshold showed damage in the Parietal Lobe, the final destination for the brain's interpretation of pain stimuli – i.e. "ouch, I was hit with a hammer", or, in phantom limb syndrome, a false interpretation of pain from an amputated foot.

Researchers expected to find abnormalities also in stress testing for pain and fatigue when challenged with riding a stationary bicycle; they did not find this on the fMRI. Instead, they found autonomic cardiac changes that could be similar to Haley's findings – namely an excessively elevated heart rate creating severe the sensation of severe anxiety. The abnormal antigravity blood pressure responders – orthostatic group - had higher anxiety scores than those with the higher pain response, again supporting Haley's findings that Gulf War Syndrome comes in different forms, perhaps due to exposure to different toxic environments on the battlefield.

Georgetown researchers support Haley's research at Southwestern Medical Center and White et al in Boston; namely, Gulf War Syndrome is not a "soft" multisymptom illness without specific hard findings. It is a hard diagnosis and a specific neurological diagnosis that is multiform in presentation with complex, but robustly abnormal, objective chemical neurotransmission abnormalities in the central nervous system.

"In previous research Baraniuk and Rayhan found differences in the white matter of the ill veterans by using an fMRI, which means there is an objective diagnosis for Gulf War Illness, they say. "You can't fake it," Baraniuk said. "It's legitimate."

"The discovery is 'huge,' says another researcher, because it will allow veterans to be quickly diagnosed via the fMRI scan. Most hospitals are equipped with the necessary MRI machines, and would just need to install the proper software and train their technicians on its use. 'We're able to say, there is something here,' says the study's lead author. 'Take these veterans seriously when they come in.'" Kelly Kennedy, USA TODAY, June 14, 2013

So how does this help the hundred thousand or so veterans still surviving with Gulf War Syndrome?

The diagnosis of Gulf War Syndrome demonstrates high **validity**, in that research shows stability of the symptomatic constellation over years and consistently predicts severe disability unresponsive so far to treatment.

The diagnosis is **reliable**, in that patients can be selected clinically based on symptoms correlated with significant neurological abnormalities on objective testing.

The diagnosis has high **specificity**, despite its seeming inchoate constellation of symptoms. Studies at Boston University; The Clinical and Translational Research Center, University of Texas Southwestern Medical Center,

Dallas and Georgetown University all demonstrate robust abnormalities on objective testing between Gulf War Patients and matched controls who are free of symptoms from Gulf War I.

What is lacking is diagnostic **sensitivity** among physicians and claims examiners who make life-determining judgments about these patients. Of course, there are psychiatric problems and abnormal psychology with patients so disabled for so long. That, however, is no longer justification to minimize and becloud their long-term, and likely permanent, total neurological disability caused by service in the Gulf War.

After testimony before the House Oversight Committee for Veterans Affairs in 1994 on behalf of The Forgotten Warrior Project, witnesses were taken to the lounge of Senator Kennedy, where we heard the Secretary of Veterans Affairs Speak. He was standing 10 feet from me and emphatically stated, “make no mistake, we know Gulf War Syndrome is a real physical disease and not just in these guys’ heads”. That’s going on twenty years now! For guys like Brown, however, the wait and lack of decisive intervention by Department of Veterans Affairs had both profound and lasting impact. Brown is not so much interested in the science; he just wants it to help him and fellow combat veterans recover. “That’s something Rayhan believes is possible if the Georgetown studies are successfully replicated and scientists can identify currently available drugs that effectively treat central nervous system disorders, or develop new medications based on that research. Rayhan is also cautious about dangling new research before a group of patients desperate for help.

“When you hear those stories, hopes and dreams they had when they were younger and to see where they are now, you realize the data has to be objective,” said Rayhan. “It can’t go overboard in terms of hope, because they’ve suffered so much.” “A New Step in Solving the Mystery of Gulf War Illness”, Rebecca Ruiz, Forbes, 6/14/2013

Sound wisdom for Dr Rayhan, because, like many diseases, there is no known treatment, but compassionate care and conscientious attention to symptomatic relief can help Mr. Brown and his hundred thousands of buddies. Until they get that treatment breakthrough, however, the main message for physicians encountering Gulf War Syndrome patients is to obey The Hippocratic Oath and “do no harm” by demeaning them as psychos or compensation-seeking vets just seeking a handout. And, the commensurate need for intelligent and respectful claims adjudication of these patients is clearly demonstrated; again, for insurance doctors and claims adjudicators alike, therefore, “do no harm”.