

**Oxidative Stress and Mitochondrial Injury in Chronic Multisymptom Conditions:
From Gulf War Illness to Autism Spectrum Disorder**

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Abbreviations:

AChEi – Acetylcholinesterase inhibitors
ALS – Amyotrophic Lateral Sclerosis
ASD – Autism Spectrum Disorder
CDC – Center for Disease Control
CFS – Chronic Fatigue Syndrome
CMs – Carbamates
DBP – Diastolic Blood Pressure
DEET – N,N-Diethyl-meta-toluamide

FM – Fibromyalgia
GWI – Gulf War Illness
GWV – Gulf War Veterans
IBS – Irritable Bowel Syndrome
MCS – Multiple Chemical Sensitivity
mtDNA – mitochondrial DNA
NO/NOS – Nitric Oxide / Nitric Oxide Synthase
OS – Oxidative Stress

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OSMD – Oxidative Stress and Mitochondrial
Dysfunction
Q10 – Coenzyme Q10

RNS – Reactive Nitrogen Species
ROS – Reactive Oxygen Species
SBP – Systolic Blood Pressure

Abstract

Background: Overlapping chronic multisymptom illnesses (CMI) include Chronic Fatigue Syndrome (CFS), fibromyalgia, irritable bowel syndrome, multiple chemical sensitivity, and Gulf War illness (GWI), and subsets of autism spectrum disorder (ASD). GWI entails a more circumscribed set of experiences that may provide insights of relevance to overlapping conditions.

Objectives: To consolidate evidence regarding a role for oxidative stress and mitochondrial dysfunction (OSMD), as primary mediators in CMI, using GWI as a departure point.

Methods: Exposure relations, character, timecourse and multiplicity of symptoms, and objective correlates of GWI are compared to expectation for OSMD. Objective correlates of OSMD in GWI and overlapping conditions are examined.

Discussion: OSMD is an expected consequence of known GWI exposures; is compatible with symptom characteristics observed; and accords with objective markers and health conditions linked to GWI, extending to autoimmune disease and infection. Emergent triangulating evidence directly supports OSMD in multisymptom “overlap” CMI conditions, with similarities to, and diagnosed at elevated rates in, GWI, suggesting a common role in each.

Conclusions: GWI is compatible with a paradigm by which uncompensated exposure to oxidative/nitrative stressors accompanies and triggers mitochondrial dysfunction, cell energy compromise, and multiple downstream effects such as vulnerability to autoantibodies. This promotes a profile of protean symptoms with variable latency emphasizing but not confined to energy-demanding post-mitotic tissues, according with (and accounting for) known properties of multisystem overlap conditions. This advances understanding of GWI; health conditions attending GWI at elevated rates; and overlap conditions like CFS and ASD, providing prospects

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for vulnerability assessment, mitigation of progression, treatment, and future prevention – with implications germane to additive and excessive environmental oxidative stressor exposures in the civilian setting.

Introduction

Chronic multisymptom illnesses (**CMI**), including chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome, multiple chemical sensitivity and Gulf War illness (**GWI**), show strong overlap¹⁻⁴. Autism spectrum disorder (**ASD**), despite little cooccurrence with **GWI** (due to military self-selection and selection), encompasses multisymptom subsets bearing muscle, gastrointestinal, sleep and other symptoms germane to **CMI**. These are suggested to reflect a condition arising from similar mechanisms in a different developmental milieu. **GWI** entails a circumscribed set of experiences that may provide insights of relevance to these overlapping conditions.

One fourth to 1/3 of US and UK personnel deployed to the Persian Gulf in the 1990-1 conflict exhibit **GWI**, established by excluding the fraction of nondeployed controls meeting the symptom portion of eligibility⁵⁻⁹. The foundation for **GWI** has been felt to elude physiological explanation^{10, 11}. **GWI** differs in exposure relations and symptom profiles from other post-war syndromes (e.g. post-traumatic stress disorder). This conflict had many exposures that were new (anthrax vaccine, depleted uranium, permethrin impregnated uniforms), unique or comparatively unique (pyridostigmine bromide nerve agent pretreatment pills, oil fires, flea collar use by some, botulinum toxoid vaccine, nerve agent exposure resulting from munitions depot demolitions), and excessive (organophosphate and carbamate pesticide use).

Oxidative stress (**OS**) and mitochondrial dysfunction (**MD**) (together **OSMD**) are closely intertwined, and each promotes the other. We evaluate characteristics of **OSMD** and **GWI**, to show that **OSMD** may underlie some, much, or most the excess of multi-symptom illness (and neurodegenerative disease) reported in Gulf War veterans (**GWV**)^{12, 13} – and civilians with **CMI**.

Method

Exposure relations, symptom characteristics, objective marker correlates, and medical conditions in GWI are examined in relation to OSMD. Evidence from OSMD in overlap conditions are brought to bear in understanding GWI, and vice versa.

Results/Review

Gulf War Illness

26-32% of GWV demonstrate chronic multi-symptom health problems and thus have GWI apparently associated with participation^{5, 7}. (That is the fraction bearing such problems, after subtracting what was “expected” based on nondeployed controls.) The excess burden lies not in more persons with single or dual symptoms, or multiple mild symptoms; but in the added fraction bearing 3 or more symptoms of moderate or greater severity⁵. The 1990-1 ground war lasted but four days; relatively few of the ~700,000 deployed US veterans experienced combat or direct combat stressors. Though some affected veterans have psychological symptoms, most do not meet criteria for psychiatric illness, and stress-related exposures lose significance in multivariable models that adjust for chemical/environmental exposures (but not the converse)^{8, 9}.

Dominant Symptoms; Symptom Multiplicity and Heterogeneity

GWV prominently features fatigue, muscle pain and weakness, and central nervous system symptoms (cognition, mood and personality). The CDC case definition requires chronic symptoms in two of three domains of fatigue, cognitive-mood, and musculoskeletal⁷. Kansas criteria require symptoms in three of six domains – fatigue/sleep, pain (muscle-joint), and cognitive-mood-neurological, gastrointestinal, respiratory and skin⁵; these also must be multiple

within the category and/or at least moderately severe, with onset since 1990⁵. Kansas criteria are more specific (fewer non-GWV meet symptom criteria).

Archetypal clinical symptoms in MD also comprise fatigue, muscle and brain symptoms “Encephalomyopathy”¹⁴⁻²⁰ is the classic manifestation of mitochondrial respiratory chain dysfunction. Over 100 distinct mtDNA mutations have been linked to brain and muscle symptoms²¹. Brain and muscle are postmitotic, with high energy demands, providing particular vulnerability^{21-24 70}.

Symptom multiplicity and heterogeneity further typify GWI. Many additional symptoms, though less frequent, also occur at markedly elevated rates^{5, 10, 25, 26}. Other CMI also commonly bear multiple symptoms, with high overlap^{2, 4}.

Such symptom multiplicity^{21, 27} and heterogeneity^{28-37 38} also characterize MD, so much that “A mitochondrial disease should be considered in the event of dysfunction of more than 2 organ systems or processes with high energy requirements”²⁷. The remaining Kansas GWI criteria -- gastrointestinal dysfunction^{16, 36, 37}, pain^{29, 31, 39}, skin^{40, 41}, sleep⁴²⁻⁴⁵, and breathing symptoms are common in MD^{43, 46}, with many further symptoms elevated in both settings. Symptom heterogeneity in MD rests on a) random somatic segregation of mitochondrial (**mt**) DNA mutations^{47, 48} and mitochondrial heteroplasmy⁴⁹⁻⁵¹: different organs bear different *prior* mtDNA mutation loads leading to different vulnerability; b) variable progression of mitochondrial defects: different mutations may *arise* in different tissues, with some more severe and/or conducive to OS that fosters more mtDNA mutations^{19, 52}; and c) clinical threshold effects^{21, 53}: symptoms arise when mtDNA mutations or resulting cell death surpass a threshold. The fraction of mutated mtDNA in an organ, the mutation severity, the energetic demands of the organ and the cell loss determine clinical consequences^{21, 54}. Symptom variability is an *inherent feature of*

MD (Even persons with familial MD may vary vastly in which symptoms are expressed - and in their timecourse of expression⁵⁵). – and an empiric feature of GWI and other CMI¹⁰. (See **Table 1a&b, Supplement Table 2.**)

Symptom latency

It is often presumed that symptoms, to relate to an exposure, must arise during an exposure, and that the exposure must show acute toxicity. (Cancer and neurodegenerative disease, familiar disease conditions rather than symptoms, represent recognized exceptions.) GWI does not behave in this fashion.

GWI is characterized by variable latency to symptoms following Gulf exposures – with many new symptoms arising well after participation, and 40% of new symptoms reportedly arising more than a year after Gulf service¹¹. **Symptoms in MD are also characterized by variable latency to onset.** MD produces (commonly) OS. OS trigger further mtDNA mutations and more MD. The severity of new mutations, and degree of heteroplasmy, determine the severity of OS production – and speed of progression. As mtDNA mutations and OS accrue, cells lose function or die, from energy depletion or OS-precipitated necrosis or apoptosis⁵⁶ – achieving phenotypic thresholds^{21, 53}. (See below for autoimmune predisposition.) Even in a kindred with heritable mtDNA defects that involved neurological problems, “the age of onset of major neurological disturbance varied from 3-70 years”⁵⁵. The principles are similar whether initial mtDNA damage is heritable or acquired; however acquired mtDNA mutations may be typified by multiple different mutations each in a low fraction^{19, 49}, which may particularly dispose to classical or “nonspecific” symptoms of MD, compatible with CMI. OS may predispose to autoantibodies and vulnerability to infection (below). Delayed symptoms may further arise from OS-promoted

autoantibodies and colonization/infection with pathogens (below); and as new OS exposures appear, to which existing OSMD provide heightened vulnerability (due to adverse OS:antioxidant defense balance). OS may promote impaired gene expression related to detoxification, in part via alterations in DNA methylation. **Add excitotoxicity?**

Exposure Associations

A range of “unrelated” exposures are linked to GWI. Acetylcholinesterase inhibitor (AChEi) exposures (organophosphates, as nerve agents and pesticides; and carbamates, as pesticides and pyridostigmine bromide nerve agent pretreatment pills) show especially strong and consistent links to health problems in GWV⁵⁷. Moreover, AChEis show a dose-response relationship to GWI (number of pyridostigmine bromide pills⁵⁷); and proximity to the Khamisiyah munitions depot demolition (sarin nerve agent plume) is linked to extent of brain atrophy and neuropsychological dysfunction in GWV^{58, 59}. Additional findings, extending to genetic evidence (such as paraoxonase variants⁶⁰. These support a causal association of AChEi to GWI⁵⁷, so mechanisms of toxicity by AChEis are of special interest. (GWV/GWI is also linked to reduced paraoxonase activity levels^{60, 61}; however low activity may be effect and/or cause, as paraoxonase is HDL-associated, and OS promotes reductions in HDL.) CMI including chronic fatiguing illness and autism have also been linked to organophosphates⁶²⁻⁶⁴, gene variants in paraoxonase^{62, 65}; and other elements of organophosphate detoxification⁶⁶, as well as low paraoxonase activity⁶⁷.

While AChEi show especially strong and consistent associations to GWI (and are also linked to other CMI), anthrax vaccine^{6, 68-70}, multiple vaccinations^{6, 68, 71-73}, and adverse reactions to vaccinations^{6, 68, 69} show generally consistent significant associations to GWI. Vaccinations are

also linked to other CMI^{64, 74, 75}. Among Gulf-era (Aug 1990-Jul 1991) non-Gulf deployed personnel, rates of “GWI” for those receiving military vaccines in that period OR 3.8 (95%CI 1.5-9.5) were intermediate between rates in non-deployed non-vaccinated (OR 1.0, the standard), and Gulf deployed (OR 10.6, 95% CI 4.9-23.1)⁷⁶ suggesting that vaccines bore a relation to illness irrespective of the Gulf setting. Depleted uranium (bearing potential heavy metal and radioactive toxicity), paints, solvents, and fumes have also shown connections to illness in some epidemiological studies^{5, 6, 26, 69, 71}. Additionally, pesticide exposures of non-AChEi classes also occurred.

The exposures linked to GWI appear “unrelated” in chemical structure and classical mechanism of action. However they share in common induction of toxicity via OSMD. Thus, AChEi toxicity and lethality are normally viewed in cholinergic terms. However in fact they are mediated by OSMD (contributing to apoptosis)^{77, 78}: the salience of OSMD in their toxicity is underscored by the relation of their lethality to impaired glutathione mechanisms; and protection from OP lethality via preexposure or immediate postexposure to relevant antioxidants in experimental animal studies⁷⁹⁻⁸¹. Vaccines, in contrast, are not known to inhibit AChE. However these, and other exposures linked to GWI, each exerts toxicity via OSMD (**Table 1a**). Further, the number of such exposures (crossing different classes) also predicted GWI¹¹ – and predicts greater OSMD⁸²⁻⁸⁵. These considerations begin to provide a framework, coupled with individual variabilities, for genesis of some cases of CMI outside the Gulf War setting.

Proposed Mechanism

OS via reactive oxygen species (**ROS**) and also reactive nitrogen species, (**RNS**), (for simplicity of exposition we designate the joint processes as “OS”) damage proteins, lipids, RNA

and DNA – particularly in mitochondria^{86, 87}, impairing mitochondrial energy production. Mitochondria are a leading target of ROS^{88, 89} due to proximity to ROS production (much of which occurs in mitochondria^{88, 90, 91}), such that mtDNA mutate at 10-1000x the rate of nuclear DNA^{92, 93}. Since all mtDNA genes are germane to oxidative phosphorylation⁹⁴⁻⁹⁶, mtDNA damage commonly hampers mitochondrial respiratory chain function, which in turn further impairs cell energy production and often further increases ROS release^{86, 87}. Reduced energy and increased ROS each cause cell (and subcellular) dysfunction and each can induce cell death, by necrosis or apoptosis^{56, 97-100}. Additionally, the further increase in ROS that is a consequence of mtDNA damage can induce further mtDNA injury – advancing a cycle of OSMD, cell energy depletion, cell dysfunction, and potentially cell loss^{86, 87, 101}. (OS also promotes MD by inhibiting mitochondrial import of essential precursor proteins¹⁰².) OS, adversely affecting the balance of OS to antioxidant defense, can increase vulnerability to, and clinical consequences of, new oxidative exposures. When enough mitochondria are dysfunctional, or enough cells dysfunctional or dead, symptoms or organ dysfunction emerge – mitochondrial “threshold effects”. (OS may have further implications via effects on DNA methylation¹⁰³ and excitotoxicity^{104, 105}, which may be magnified in settings of low mt EN production^{106, 107}.) It is reiterated that major Gulf exposures are known to produce toxicity via OSMD producing expectation of cell dysfunction and cell death. (Note that organophosphates further produce mitochondrial and energetic compromise through toxicity to microtubules¹⁰⁸, interfering with mitochondrial biogenesis¹⁰⁹ and transport¹¹⁰. Mitochondria are dynamic rather than static organelles^{111, 112}.)

Downstream Effects - OS-induced Mechanisms

OS also depress vitamin D (vitD), vitD receptor expression and mitochondrial vitD hydroxylase activities^{113, 114}. Low vitD and altered receptor function are linked to risk of autoimmune disease¹¹⁵⁻¹¹⁹. Autoimmune markers are elevated in GWI^{120, 121}, as well as in other CMI^{74, 75, 122}). Vaccines have been linked to illness in GWV^{6, 68-71} and in some cases chronic fatigue. (They are also a politically and scientifically contentious proposed contributor to ASD.) Reactogenic vaccines are a source of OS^{82♦}. Additionally, vaccine adjuvants (based on aluminum – which is an oxidative stressor, as are components of vaccine preservatives and adjuvants) are expressly incorporated for the purpose of enhancing immune/antibody reactions – in principle to the intended administered antigen, but they may also adjuvant native protein and nonprotein substances. Adjuvants associated with vaccines remain resident in the body and may continue to exert adjuvant effects, promoting “autoimmune syndromes induced by adjuvants” (“ASIA”)^{122, 125-128}. Low vitamin D activity (see above) is also linked to increased infection vulnerability¹²⁹⁻¹³⁴. These factors, coupled with EN deficits and OS-reduced NK activity^{120, 135}, may account for increased autoantibodies, and increased evidence of a range of infectious agents (and antibodies to them), in GWI and associated exposures^{120 136-139} – and other CMI^{74, 75, 140} including ASD¹⁴¹⁻¹⁴³. These contribute further to symptom heterogeneity and latency.

Excitotoxicity is another potential downstream mechanism. Oxidative stress enhances excitotoxin effects, such as DCD (delayed calcium deregulation) which “precedes and predicts” cell death¹⁴⁴. So, too, does mitochondrial calcium accumulation¹⁴⁴. Moreover, excitotoxins in

♦ Squalene has been politically contentious in GWI. One is not impelled to suppose that squalene-adjuvanted variants of anthrax vaccine were used, in order for squalene antibodies to arise: squalene occurs naturally in the body and may also be present in small amounts in vaccines as a contaminant¹²³. McDonald T. MOD Anthrax Vaccine Contains Squalene. "Tonight with Trevor McDonald", March 17, 2003, ITV1, 8PM 2003 Mar 17, 2003, 124. Rodriguez PM. Squalene presence confirmed by FDA. Insight 2000; <http://www.insightmag.com/news/2000/10/30/TheLastWord/Squalene.Presence.Confirmed.By.Fda-213345.shtml>.

turn cause oxidative stress and mitochondrial impairment, which is a major mediator of excitotoxin neurotoxicity¹⁴⁵.

Other sequelae of oxidative stress and mitochondrial dysfunction further contribute to cell dysfunction, cell death, and symptoms.

Differential vulnerability

Differential vulnerability – in which some but not other servicepersons with apparently similar exposures have developed GWI (or CMI) – emerges naturally from an OSMD conceptualization. Differences in genetic and nongenetic biological detoxification capability^{60, 66, 106, 146-150}, total OS load and pro-oxidant/antioxidant balance¹⁴⁷, prior inherited or acquired mitochondrial mutation load or heteroplasmy status^{47, 49, 54, 95}, heritable vulnerability to autoimmune disease, and perhaps prior loss of cells in postmitotic organs, provide for individual differences in vulnerability to development of symptoms following Gulf- (or civilian-) associated OS exposures.

Objective findings

Routine laboratory tests are not classically abnormal in GWV (or CMI) or in OSMD. **Table 1a&b** depict those objective findings that have been reproducibly documented in GWV (demonstrated in at least two studies). In each case the objective finding has a demonstrated relation to OSMD (generally OS, which is more commonly tested). These include depressed paraoxonase (PON1)^{60, 61, 151}, increased gamma glutamyl transferase (GGT)^{152, 153}, reduced natural killer cell activity^{120, 154}, blunted heart rate variability,^{155, 156} increased autoantibodies^{120,}

¹²¹, and increased coagulation activation^{157, 158}. Each has been reported in other CMI. And each is a documented consequence of OSMD.

Associated Health Conditions

In addition to symptoms, several conditions have been found to be elevated in GWV. These include hearing loss, hypertension, and amyotrophic lateral sclerosis (**Table 1a&b**). These conditions are also known to bear particularly strong relations to OSMD.

These findings are compatible with a common mechanism involving OSMD, targeting different tissues to varying degrees. Motor neurons are one possible (though relatively rare) target tissue, engendering ALS when affected. However other distributions of effect result in multisymptom conditions (GWI-CFS-spectrum conditions), metabolic syndrome features¹⁵⁹, and a range of other conditions, which accompany one another at elevated rates^{2-4, 160}.

Triangulating Evidence from CMI

Patients with other CMI commonly have multiple “unexplained” symptoms spanning many domains. These conditions have substantial overlap with one another -- and with GWI^{2-4, 6, 26, 160-164} (see **Table 1a&b**) consistent with the hypothesis put forth here that common OSMD mechanisms target multiple domains, with factors like heteroplasmy (among others) producing differential vulnerability of potential target tissues.

Reported odds ratios for CFS range from ~4 to ~40 in GWV vs nondeployed controls (**Table 1a&b**), suggesting shared mechanisms at least for subsets of CFS. CFS patients show elevated OS¹⁶⁵, an exaggerated prooxidant response to new OS¹⁶⁶ (which we propose may signify a preexisting adverse prooxidant:antioxidant balance), and activation of coagulation

pathways¹⁵⁷ (the relation to oxidative stress is discussed above). Moreover, OS levels correlate with symptoms in CFS¹⁶⁷. Evidence also favors a relation of CFS to MD: functional status in CFS correlates with carnitine levels^{168, 169}; and a subset of CFS cases show elevated lactate with exertion, and delayed ATP recovery after exercise, on magnetic resonance spectroscopy¹⁷⁰, with OS believed to underlie the energetic effects¹⁷¹. Furthermore, an “ATP profile test” of mitochondrial function successfully (and completely) discriminated CFS cases, defined by the CDC criteria which require multisymptom illness (most similar to GWI)¹⁷². Additionally, CFS patients have been reported to differ from controls in genetics related to mitochondrial function¹⁷³, energetics¹⁷³ and apoptosis¹⁷⁴. Fibromyalgia and irritable bowel syndrome²⁶ – which are increased (~2-5 fold) in GWV – also bear evidence of a link to OSMD^{39, 175-177} (**Table 1a&b**). So does ASD^{67, 103, 148, 149, 178-182}. MCS has been linked to mutations in genes for glutathione-S-transferase (GST), which protects from oxidative stress by conjugating glutathione, detoxifying “a large range of compounds generated by reactive oxygen species induced damage to intracellular molecules”.¹⁴⁷ It might be conjectured that apparent instances of exposure-triggered MCS may entail exposure-triggered increased endogenous OS production (through mechanisms detailed above); and perhaps also exposure-triggered modifications in gene expression of key detoxifying enzymes.

MCS, “sensitivity” to chemicals – and also medication intolerance¹⁸³ – are significantly more common in GWV^{5, 6, 25, 26, 160, 184, 185} and in overlap conditions^{2-4, 186}. Both chemical (**Table 3**) and drug adverse effects are commonly mediated through OSMD¹⁸⁷⁻¹⁹⁰. (MCS, like GWI and ASD cited elsewhere, shows altered genetic profiles of PON^{60, 191}.) OSMD provides an account of why medication and vaccine adverse effects at the time of the Gulf were associated with increased risk of developing GWI^{6, 68, 192, 193}. These adverse effects signal less favorable OSMD status at the time of exposure *and or* greater oxidative

stressor exposure, promoting OS dominance over antioxidant defences, which may both predict and help mediate the development of multisymptom GWI in the setting of new OS exposure.

Other conditions have been linked to OSMD but have not (yet) been evaluated in GWI. An elevation in a number of these conditions in GWI represents a prediction of this theory. Some markers and objective conditions have been linked to GWI and OSMD, and at least one CMI; but have not been evaluated in other CMI. A prediction of this theory is that many, when examined in studies with sufficient power, will be seen in other CMI.

Discussion

An explanation focused on OSMD accounts for GWI, and other CMI. Put forth is a proposition by which exposures to oxidative stressors, in part via cumulative MD, in part via autoimmune effects in vulnerable individuals, in part via apoptosis/cell loss leading to coagulation activation, may increase risk of a range of chronic health problems in GWV – including the multisymptom spectrum termed GWI – and other CMI. Such an account accords with known exposure relations of otherwise unlike character; explains symptoms with otherwise unexplained organ tropism, with otherwise unexplained protean character and with otherwise unexplained variable timecourse to onset. It fits with the otherwise unexplained range of objective markers linked to these conditions that cross classical boundaries. It explains observed associations to other health conditions of varying character; and accounts for increases in multisymptom “overlap” conditions (and for overlap of these syndromes with one another). A role for OSMD might be predicted on “first principles” (known pathophysiological effects of Gulf Exposures; and known clinical sequelae of these effects)¹³. However there is now direct evidence of a relation of OS and MD to each of the conditions to which GWI relates, providing further triangulating support for a role for OS and MD extending to GWI.

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CMI has not traditionally been thought to include autism spectrum disorder (ASD); but multisymptom cases of ASD may reflect manifestations of similar processes operating at a different developmental timepoint. ASD not uncommonly comprises multiple symptoms across a similar spectrum,^{181, 194-197} with purported links to similar exposures, and observed relations to OSMD^{106, 149, 180, 182, 198-207}. (All ASD need not cohere with these principles.)

Accrued evidence now more vigorously supports a paradigm by which OS and MD conduce to one another, disposing to GWI or other CMI. These mechanisms may operate in some, many or possibly most CMI. The Gulf War setting has its distinctive constellation of OS exposures. However the pathophysiological principles articulated, beyond their potential relevance to GWI, yield a new lens with which to review a range of important, interrelated health conditions – including but not confined to “overlap” CMI conditions often considered to be unexplained – and to understand their relationship to one another – in the military setting, and outside of it.

Figure 1: Oxidative Stress and Mitochondrial Dysfunction Mediate the Link between “Unrelated” Exposures and Symptoms

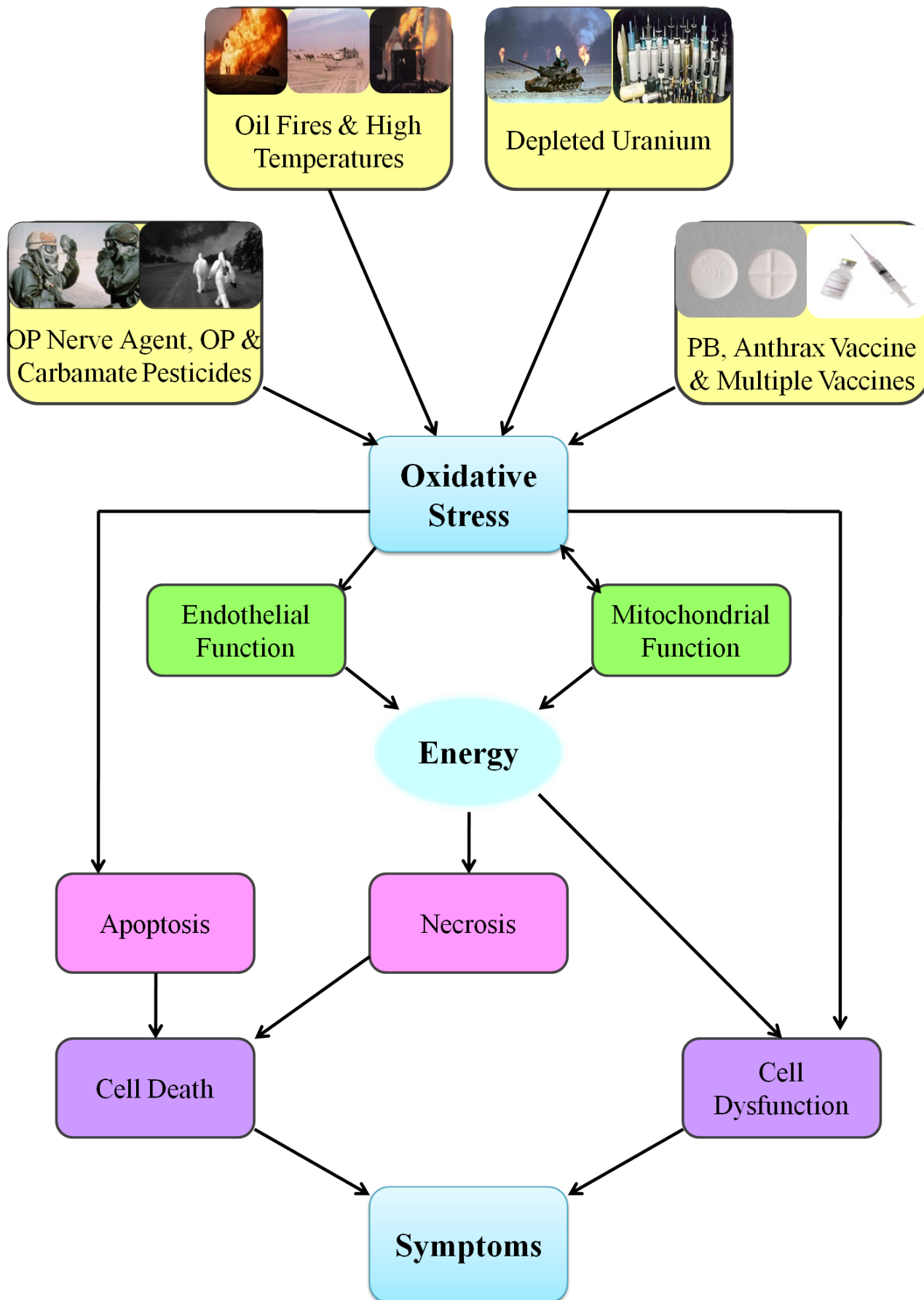


Table 1. Overview

	GWI	OSMD	CMI
Dominant Symptoms	Symptoms protean but focus on fatigue, cognitive-mood, musculoskeletal, also gastrointestinal, sleep, neurological	Symptoms protean but focus for MD on fatigue, cognitive-mood, musculoskeletal, also gastrointestinal, sleep, neurological	Symptoms protean with emphasis defined by the condition (fatigue for CFS; muscle for FM; GI for IBS; CNS/"cognitive" for ASD; chemical sensitivity for MCS) but very high overlap
Symptom multiplicity/heterogeneity	Symptoms multiplicity with high heterogeneity	Symptoms multiplicity with high heterogeneity	High heterogeneity of symptoms
Symptom Latency	Variable Latency to Symptom Onset	Variable Latency to Symptom Onset	Variable Latency to Symptom Onset
Exposure Associations	Include OPs/ acetylcholinesterase inhibitors, paraoxonase gene variants, vaccines	Causes include OPs/acetylcholinesterase inhibitors, paraoxonase gene variants, vaccines	Include OPs/ acetylcholinesterase inhibitors, paraoxonase gene variants, vaccines
Objective Findings	Include autonomic dysfunction, reduced natural killer cell activity, coagulation	Include autonomic dysfunction, reduced natural killer cell activity, coagulation	Include autonomic dysfunction, reduced natural killer cell activity ^{208, 209} ,

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	activation, elevated autoimmune markers, elevated GGT, low paraoxonase activity	activation, elevated autoimmune markers, elevated GGT, low paraoxonase activity	coagulation activation ²¹⁰ , elevated autoimmune markers ⁷⁴ , ^{75, 122} , elevated GGT ²¹¹ , low paraoxonase activity ⁶⁷
Related conditions	Include CMI (except ASD). Also include hypertension, hearing loss, ALS	Include CMI (extending to ASD). Also include hypertension, hearing loss, ALS	Include hearing loss.

Table 1a. Gulf War Associations

Associated Characteristic	Seen With	
	Gulf War Illness (also other CMI)	Oxidative stress ↔ mt Dysfunction
Exposure Associations		
Acetylcholinesterase inhibitors strongly associated	Yes ^{6, 57}	Yes ^{77, 78}
Reactogenic vaccines also consistently associated	Anthrax vaccine associated ^{6, 69} Vaccine adverse effects associated ^{6, 193} Multiple vaccinations associated ^{6, 68, 71, 72}	Reactogenic vaccines associated with OS ⁸² ; Anthrax vaccine among the most reactogenic of vaccines ²¹² Aluminum (vaccine adjuvants), mercury (thimerosal preservatives) linked OS, impaired antioxidant defense against other exposures, and MD ²¹³⁻²²⁸
Multiple other exposures are associated	See Supplement Table 1	1. See Supplement Table 1
Symptom Characteristics		
Brain and muscle dominate	Yes ⁷	Yes ²²
Fatigue and fatigue with exertion prominent	Yes ^{5, 7, 25, 26}	Yes ^{46, 172, 229, 230}
Symptoms are protean spanning many domains	Yes ^{5, 25, 26}	Yes ²³¹
Symptoms differ from person to person	Yes ^{5, 7, 25, 26}	Yes ^{55, 232-234}
Latency to symptom onset is variable, often prolonged, differs across individuals and differs across symptoms within an individual	Yes ¹¹	Yes ⁵⁵
Individual Symptoms Associated	See Supplement Table 2	See Supplement Table 2
Objective Findings		
Routine labs generally unremarkable	Yes	Yes
PON genotype differences present	Yes*** Other CMI ¹⁹¹ add ASD, CFS	Yes
GGT elevated (marker of oxidative stress)	Yes ^{152, 153} (other OS markers not examined) Other CMI:	Yes ^{235, 236}
PON1 activity reduced	Yes ^{60, 61, 151} Other CMI:	Yes ^{237, 238}
Natural killer cell activity reduced	Yes ^{120, 154} Other CMI:	Yes ^{135, 239-241}
Heart Rate variability blunted	Yes ^{155, 156}	Yes ^{242, 243}
Other autonomic abnormalities present	Yes ^{244, 245} Other CMI:	Yes ^{31, 246, 247}
Coagulation markers elevated	Yes ^{157, 158} Other CMI:	Yes ²⁴⁸⁻²⁵¹ (OS promotes apoptosis ^{98, 99, 252} ; which activates coagulation pathways ²⁵³)
Autoimmune Markers Elevated	Yes ^{120, 121} Other CMI: ^{74, 75, 210} autism autoantibodies check	Yes ADD CITS ²⁵⁴ (May be partly adaptive ^{255, 256})

Exposures:

AChEi are particularly potent in inducing OS and MD⁷⁷ – and particularly strong consistent predictors of GWI. AChEi exposures, moreover, were also commonly recurrent when they occurred; and in addition, they cause MD by means beyond OS (such as microtubule toxicity^{257, 258}). The central role of OS in mediating AChEi

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toxicity is underscored by findings that pretreatment (or immediate posttreatment) with antioxidants protects against AChEi-induced lethality (and enhances recovery) in animals⁷⁹⁻⁸¹. Anthrax vaccinations and multiple vaccinations are the next most strongly and consistently linked to GWI, in epidemiologic evidence²⁵⁹. These are tied, through aluminum-based adjuvants^{218, 219, 222-224, 226, 260, 261} and mercury (and other) preservatives²²⁵, to OS and MD (**Table 1, Supplement Table 1**) – as well as to inhibition of glutathione production, reducing antioxidant defense against other exposures^{219, 222, 225}. Each additional exposure class presumptively inculcated in GWI is known to promote OS^{82-85, 226, 262-264}.

Markers:

GGT is an enzymatic antioxidant^{265, 266}; elevations serve as an early marker of OS²⁶⁷ including AChEi exposure^{265, 268}. PON1 is an antioxidant enzyme (also specifically involved in organophosphate detoxification²⁶⁹) whose activity is depressed in settings of elevated OS²³⁷. PON1 was depressed in GWV generally (relative to military controls) – and particularly so in those with GWI or more symptoms^{60, 61, 151}. Natural killer activity is reduced with OS and increased with antioxidants^{135, 239, 240}. Blunted heart rate variability has been linked to OSMD^{242, 243}. Activation of the coagulation system relates to OS^{248, 249, 251, 270}. Both OS^{98, 99, 252} and MD^{271, 272} each foster apoptosis; which exposes phosphatidylserine at the cell surface, activating coagulation pathways²⁵³. Activation of the coagulation system has been repeatedly observed in Gulf War veterans.^{157, 158} OS also depresses vitamin D (vitD), vitD receptor expression and mitochondrial vitD hydroxylase activities^{113, 114}. Low vitD and altered receptor function are linked to risk of autoimmune disease¹¹⁵⁻¹¹⁹.

OS – oxidative stress; GWV – gulf war veterans; GWI – gulf war illness; MD – mitochondrial dysfunction

Table 1b. Associated Conditions are Compatible with OSMD

Associated Conditions	Linked to GWV	Linked to OSMD
Chronic Fatigue syndrome	Yes ^{5, 6, 26, 160, 164, 273}	Yes ^{165-167, 170-172, 274-276}
Fibromyalgia	Yes ^{5, 164, 273}	Yes ^{39, 175-177, 277, 278}
Irritable Bowel syndrome	Yes ²⁶	Yes ²⁷⁹
Multiple Chemical Sensitivity	Yes ^{5, 6, 25, 26, 160, 184, 185}	Yes ¹⁴⁷
<i>Autism Spectrum Condition</i>	<i>No – different developmental timeline</i>	Yes ^{67, 106, 107, 148, 180-182, 200, 280, 281}
Hypertension	Yes ^{6, 26, 153, 282, 283}	Yes ²⁸⁴⁻²⁸⁹
Weight gain	Yes ^{7, 26, 153}	Yes ²⁹⁰⁻²⁹³
Amyotrophic lateral sclerosis	Yes ²⁹⁴⁻²⁹⁶	Yes ²⁹⁷⁻³⁰⁰
Hearing loss / tinnitus	Yes ^{5, 6, 10, 26}	Yes ^{28, 234, 301-307}
Fracture risk and reduced bone formation	Yes ^{308, 309}	Yes ³¹⁰⁻³¹³

Significant elevations in self-reported hearing loss after 1990 or 1991 in GWV vs control groups have been reported^{5, 6, 10, 26}. (However obviously, even with military controls, there are uncertainties regarding noise exposure comparability. Additionally, formal testing has not yet been undertaken.) Hearing loss deemed “age-related” and “noise-related” is powerfully linked to OSMD³⁰³⁻³⁰⁶. Accelerated hearing loss is common in MD^{28, 34, 314-322}, cited as among the most common symptoms of mitochondriopathy, together with fatigue and muscle symptoms³⁰. And chemical exposures have been linked to both hair cell damage and *noise*-related hearing loss^{323, 324}.

GWV demonstrate increased incident hypertension in a range of studies (**Table 1a&b**)^{6, 26, 153, 282}. Hypertension, too, is a condition with powerful relationship to OSMD^{284-287, 325, 326}. Indeed an evaluation of mitochondrial pedigrees estimated the fraction of patients with hypertension potentially due to mtDNA mutation involvement at 55% (95% CI 45-65%)²⁸⁵. Analogous to the Gulf War situation, increased blood pressure has been previously associated with environmental OS exposures. For instance, both arsenic and lead are reported to mediate their toxicity via OS³²⁷⁻³²⁹; and exposure to each arsenic (e.g. in the water supply)^{330, 331} and lead^{327, 328} have been linked to increased rates of hypertension. Hypertension and hearing loss are both common “age-related” conditions.

In contrast, amyotrophic lateral sclerosis (**ALS**) is an uncommon but serious age-related condition. ALS has been reported in several studies to have increased incidence in GWV (**Table 1a&b**). This condition has been conceptualized as resulting from “oxidative damage to mitochondrial DNA leading to the accumulation of mitochondrial DNA mutations”³³² – in this case targeting the spinal cord – compatible with the mechanism I propose for GWI more generally – and other GWV associated conditions. Extensive evidence links ALS to OSMD^{297, 299, 300, 333-343}. Moreover, low concentrations and mutations of paraoxonase, central to organophosphate (AChEi) detoxification, have been linked to ALS³⁴⁴⁻³⁴⁷ – and to GWI^{60, 61, 151, 348} (as well as to GWI-like multisymptom illness following organophosphate exposure outside the Gulf setting^{62, 349, 350}), further

* (Noise “sensitivity” has been noted as a some-time feature of multiple chemical sensitivity, and is also noted in ASD. Since both conditions have been linked to impaired antioxidant defenses¹⁴⁷. Schnakenberg E, Fabig KR, Stanulla M, et al. A cross-sectional study of self-reported chemical-related sensitivity is associated with gene variants of drug-metabolizing enzymes. *Environ Health* 2007;6:6, 180. Geier DA, Kern JK, Garver CR, et al. Biomarkers of environmental toxicity and susceptibility in autism. *J Neurol Sci* 2008, 198. Jill James S, Melnyk S, Jernigan S, Hubanks A, Rose S, Gaylor DW. Abnormal Transmethylation/transsulfuration Metabolism and DNA Hypomethylation Among Parents of Children with Autism. *J Autism Dev Disord* 2008, 280. Bradstreet JJ, Smith S, Baral M, Rossignol DA. Biomarker-guided interventions of clinically relevant conditions associated with autism spectrum disorders and attention deficit hyperactivity disorder. *Altern Med Rev* 2010;15:15-32. this “sensitivity” to both noise and chemicals could signify actual vulnerability to damage at lower levels than would be harmful in others.)

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propelling the case for OSMD in GWI. By the mechanisms elucidated here (and previously elaborated by us in a different setting of exposure-induced ALS³⁵¹), although spinal cord motor neurons are the primary condition-defining target, mitochondrial dysfunction in sporadic ALS *should not be confined to spinal cord motor neurons* but should (statistically) be evident in other tissues, particularly energetically demanding (and thus mitochondrially vulnerable) brain and muscle. Indeed, recent studies show that mitochondrial pathology in ALS extends to skeletal muscle³⁵²⁻³⁵⁷ and symptoms extend to cognitive function in about half of cases^{358, 359}.

Mounting evidence supports a connection of OSMD^{290-293, 360, 361} to metabolic syndrome (each has been conceptualized as a unifying mechanism^{293, 361}), of which hypertension is one component. Consistent with this, studies have also reported increased incident weight gain in GWV vs controls^{7, 26, 153}. Assessment for other elements of metabolic syndrome in GWV has not yet been undertaken, but increased metabolic syndrome represents a prediction of this model.

Table 3. Predictions

	Observed with Oxidative Stress/ Mitochondrial Dysfunction	Preliminary Evidence or Comment
Other markers of oxidative stress and mitochondrial dysfunction will be elevated	Yes ⁵⁴	True for chronic fatigue syndrome ^{167, 171, 172} , a related condition that is elevated in GWV ^{5, 6, 26} True for ASD
Genetic risk markers related to mitochondrial function, antioxidant defense, energetics, and apoptosis will be identified	Yes, by definition	Gene associations related to mitochondrial function, energetics and apoptosis have been reported for chronic fatigue syndrome ^{66, 173, 174, 276} a related condition that is elevated in GWV ^{5, 6, 26} . Deletions in genes for glutathione-S-transferase enzymes (leading to loss of protection against oxidative stress) are strongly and significantly linked to multiple chemical sensitivity ¹⁴⁷ Gene variants in paraoxonase have been observed in both GWI and ASD**, and glutathione-related variants among others in ASD ^{148, 198, 362}
GWV will have increased rates of adverse effects with many medications and interventions because many adverse effects are mediated via oxidative stress and mitochondrial problems ¹⁸⁷⁻¹⁹⁰	See Comment. Examples of drugs with adverse effects mediated by oxidative stress include acetaminophen, aminoglycosides, fluoroquinolones, amiodarone, nonsteroidal anti-inflammatory agents, chemotherapeutics, ^{83, 188, 190, 363-378}	Increased drug adverse effects have been observed in irritable bowel syndrome ³⁷⁹ – a condition elevated in GWV ²⁶ and linked to oxidative stress ²⁷⁹ . Regression reported by some parents following vaccinations in cases of ASD may be a <i>consequence</i> of impaired detoxification. (Such vaccination may boost the oxidative burden, however, and potentiate the process.)
New oxidative stressor exposures – beyond medications and medical interventions, though those merit separate mention - will have disproportionate adverse impact in exposed and particularly symptomatic GWV and CMI		Prooxidant-antioxidant balance will be adversely affected, disadvantaging ability to defend against new oxidative stressors.
Endothelial dysfunction will arise at elevated rates	Endothelial dysfunction is strongly linked to oxidative stress ³⁸⁰	
Hepatic steatosis will develop at elevated rates, as will ectopic fat deposition in other locations	Hepatic steatosis relates strongly to oxidative stress ^{381, 382} .	
<i>Low HDL and high triglycerides will emerge</i>	<i>These conditions (and all elements of metabolic syndrome) are linked to oxidative stress^{290, 383} and mitochondrial dysfunction²⁹²</i>	
<i>Free fatty acids will be elevated</i>	<i>Elevated free fatty acids are linked to oxidative stress³⁸⁴</i>	
Metabolic syndrome as a whole will arise at elevated rates	Metabolic syndrome is linked to oxidative stress ^{290, 291} and mitochondrial dysfunction ²⁹²	As above, weight gain and hypertension are already reported at elevated rates. Diabetes prevalence shows variable trends likely due to selection of diabetics out of deployment to high risk areas.
Rates of diabetes will rise to first match then exceed rates in nondeployed (those with diabetes were disproportionately nondeployed)	Diabetes, like metabolic syndrome, is strongly linked to oxidative stress (as effect but possibly also cause) ³⁸⁵ and mitochondrial dysfunction ^{287, 386}	This prediction is made despite mixed direction of trends in diabetes rates in published studies ^{5, 26} . It is predicted that a clear increase will emerge.
Rates of cardiovascular disease and particularly peripheral arterial disease will emerge at an elevated rate as GWV age	These conditions, and especially peripheral arterial disease, are associated with oxidative stress ³⁸⁷⁻³⁸⁹ and mitochondrial dysfunction ³⁹⁰⁻³⁹²	
Parkinson’s disease will emerge at an elevated rate as GWV age	Parkinson’s disease is linked to oxidative stress and mitochondrial dysfunction ^{393, 394}	Like ALS (and Gulf War illness), Parkinson’s disease bears an association to polymorphisms in paraoxonase; and exposure to pesticides ³⁹⁵⁻³⁹⁹
Elevated “depression” diagnoses will be found to disproportionately focus on somatic symptoms	Somatic symptoms in depression have been found to serve as markers for mitochondrial dysfunction. ⁴⁰⁰	“Depression” has been reported to be elevated in GWV ²⁶ . GWV have many somatic symptoms that will contribute to elevated scores in depression scales.
“Age-related” hearing loss and tinnitus will be demonstrated to occur at elevated rates	302, 306, 314, 323, 324	GWV report physician-diagnosed tinnitus at elevated rates ²⁶
Other diagnoses linked to oxidative stress will occur at elevated rates		Some reports suggest increased cancer of some types ²⁸² and cancer death in Gulf War

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		veterans ^{401, 402}
<i>Exposed</i> GWV who do not meet criteria for GWI will nonetheless show statistical abnormalities in markers of oxidative stress – and sequelae of oxidative stress (perhaps intermediate between unexposed and those with GWI)		Asymptomatic persons with mt dysfunction at low heteroplasmy rates nonetheless show increased oxidative stress, proportional to the heteroplasmy level ⁵⁴ .

GWI – gulf war illness; GWV – gulf war veterans; ALS – Amyotrophic lateral sclerosis;

* Those with GWI have many somatic symptoms that will contribute to elevated scores in depression scales.

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