

Scientific Medical Evidence for Chemical Sensitivity:

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Multiple Chemical Sensitivity (MCS) is actually **Chemical "Injury"** (biological Molecular Damage that persists after exposure and increases vulnerability to future exposures to a wide variety of chemical instigators). It is not just "Sensitivity" (which would return to normal after exposure has ceased). (The "MCS" label can be misleading.) This is discussed below.

Established Diagnostic criteria for Multiple Chemical Sensitivity (MCS):

The top **6 consensus criteria** defining MCS, supported by research definitions and published literature review, have been defined as:

1. A chronic condition (>6 months),
2. With symptoms that recur reproducibly with re-exposure,
3. In response to low levels of exposure (not bothersome to others),
4. To multiple unrelated chemicals,
5. Improvement when incitants are removed (until re-exposure), and
6. Symptoms occur in multiple organ systems.

(*Arch Environ Health. 1999 May-Jun;54(3):147-149.*)

MCS (i.e., **Chemical Injury**) can involve any organ system, especially the nervous system, which is most sensitive to damage (Toxic Encephalopathy & Sensory Nerve Inflammation), but also respiratory (Reactive Airways) and musculoskeletal (Fibromyalgia) systems, energy production (Chronic Fatigue), and digestive and skin sensitization. These related conditions are often diagnosed and treated separately (as if they were "separate diseases"), but they satisfy the MCS criteria above with multiple organ system involvement (although one organ system often predominates). (*The Toxicant Induction of Irritant Asthma, Rhinitis, and Related Conditions*, WJ Meggs, Ed, © Springer Science+Business Media, LLC, 2013, Ch 1.)

Electrohypersensitivity (EMF sensitivity) was also shown to be a variant of MCS, with inflammation-related increase of histamine, oxidative stress, autoimmune response, and peroxynitrite. (*Rev Environ Health. 2015;30(4):251-71.*)

Biochemistry of MCS triggering:

In allergy reactions, specific environmental proteins bind to IgE antibodies on mast cells of the immune system. In chemical sensitivity, non-specific low molecular weight chemicals bind to chemical receptors on sensory nerve C-fibers (supplying the respiratory tract, digestive tract, skin, etc, depending on path of entry). In both cases, inflammatory signaling molecules are released to protect the body from the "invaders", resulting in similar symptoms. In both allergy and chemical sensitivity, chronic/repeated exposures lead to adaptation changes — repeated exposures increase the severity of biological reactions to defend against a persistent "threat to survival". (Penicillin allergy reactions become more severe and dangerous with repeated exposure.) Chemical sensitivity is not the same as "allergy" and is not detected by allergy testing, because the triggers are different (on sensory nerve cell endings rather than immune cells). (*Meggs WJ, Toxicol Ind Health. 1999 Apr-Jun;15(3-4):331-8.*)

Central nervous system functions depend on excitatory neurotransmission signals controlled by NMDA (N-methyl-D-aspartate) receptors on the cell membranes. NMDA receptors are ion-

channel gates into the cell, activated by a glutamate signaling molecule to open a voltage-dependent flood of positive-charge ions that trigger the cell. These receptors help regulate nerve connections and memory function. Over-activation of NMDA receptors overworks and damages the cell structures by oxidative stress, leading to excitotoxicity, which promotes neurodegenerative disorders. (*Furukawa H et al, Nature. 2005 Nov 10;438(7065):185-92.*)

Sensitivity in MCS individuals appears to be at least 2 orders of magnitude (100x) greater than in normal individuals. Evidence in MCS shows persistent excessive activity of NMDA cell-activating receptors in affected organ systems. Four NMDA sensitizing mechanisms were described to explain such heightened sensitivity (Pall ML, FASEB J. 2002 Sep;16(11):1407-17.):

- Inflammation signaling molecules induce nitric oxide production (measurable in breath analysis), which stimulates glutamate release (a neurotransmitter signaling molecule), creating excess peroxynitrite as a cell metabolism byproduct (which is damaging if not quickly neutralized by the SOD enzyme) (*See "Vicious Cycle" diagram below*);
- Excess peroxynitrite damages the cell's mitochondria (the cell's "power plants") and degrades the cell's ATP fuel production, increasing NMDA activation to defend the cell;
- Peroxynitrite also increases permeability of the blood-brain barrier, allowing organic chemicals to enter the central nervous system; and
- Nitric oxide inhibits cytochrome P450 enzymes (a detoxifying mechanism).

These mechanisms form a positive feedback loop provoking chronic over-activation of cell function in defense against the toxic "invader". The persistent excess of peroxynitrite causes progressive damage to the cell's biological structures including cell membranes and mitochondrial membranes, faster than the cell's maintenance mechanisms can repair the damage and neutralize the peroxynitrite. With this chronic over-activation, the toxic damage does not "disappear" after an exposure episode has passed. This damage is "Injury", not just "Sensitivity".

Multiple classes of toxic chemicals are implicated in MCS (solvents, volatile organic compounds, formaldehyde, carbon monoxide, pesticides, organophosphates, and carbamates, all correlated with modern industrial development). They can all produce a common molecular biological response: provoking excessive NMDA activity that produces excess peroxynitrite that damages cell function in the involved organ systems. (*"Multiple Chemical Sensitivity: Toxicological Questions and Mechanisms" (review by ML Pall), in General and Applied Toxicology, 3rd Ed, pp.2302-2352, Nov 2009*)

A dose-response relationship was found between occupational formaldehyde exposure and DNA strand breaks (genetic damage) in the lymphocytes (white blood cells) of plywood workers. The severity of white blood cell changes in an 8-hour work shift formaldehyde exposure was correlated with the level of prior formaldehyde exposure in the workplace. (*Lin D et al, J Occup Health. 2013;55(4):284-91.*)

Genetic associations for susceptibility to environmental triggers:

Several genetic differences were found between MCS cases and controls in genes involved in detoxifying contaminants. Women who were homozygous (from both sides of the family) for genetic variation in 2 specific detoxification genes, CYP2D6 and NAT2 (the "rapid acetylator" form), were 18 times more likely to have MCS. CYP2D6 encodes for enzymes that either activate or detoxify many toxic chemicals and drugs by making them more water soluble. NAT2

encodes for enzymes that metabolize drugs and toxic chemicals including aromatic amines (many of which are known carcinogens). (McKeown-Eyssen G, *Int J Epidemiol.* 2004 Oct;33(5):971-8.)

A genetic variation of the gene encoding the PON1 enzyme, which metabolizes organophosphate chemicals, was associated with developing chronic neurological symptoms in 1991 Gulf War veterans (an MCS-like illness). (Haley RW et al, *Toxicol Appl Pharmacol.* 1999 Jun 15;157(3):227-33; Furlong CE. *Genome Res.* 2000 Feb;10(2):153-5.)

MCS patients were significantly more associated with genetic variation of SOD2 (an important anti-oxidant enzyme that protects mitochondria, the "power plants" in cells). (Cui X et al, *PLoS One.* 2013 Aug 13;8(8):e73708.)

Genetic variation of the nitric oxide synthase (NOS) enzyme, important for producing nitric oxide in response to inflammatory disorders, is associated with increased risk of MCS. (De Luca C et al, *Mediators Inflamm.* 2015;2015:245308.)

Diagnostic testing:

25-32% of 1991 Gulf War veterans developed persisting symptoms (called Gulf War Illness, GWI), lasting for years and including any combination of fatigue, headaches, cognitive dysfunction, musculoskeletal pain, and respiratory, gastrointestinal and dermatologic complaints (multiple organ system involvement). These persisting health problems (a massive epidemic of MCS) correlated with history and severity of massive exposures to a variety of toxic chemicals in the war zone. Psychiatric etiologies were ruled out by documentation of biochemical and brain structural changes. Genetic susceptibilities in detoxification enzymes are suspected risk factors. (Veterans call these chemical-exposure health consequences "toxic wounds".) (White RF et al, *Cortex.* 2016 Jan;74:449-75. doi: 10.1016/ PMID: 26493934)

Epidemiologic studies of Gulf War veterans have identified excess rates of prominent neurological symptoms including persistent headache, memory and concentration difficulties, dizziness, and mood and visual disturbances. ALS (a fatal neurologic disease) affects Gulf War veterans at twice the rate of non-deployed veterans. Gulf War veterans downwind from chemicals in the 1991 Khamisiyah demolitions have reduced white matter brain volume on MRI scans, and have died from brain cancer at twice the rate of other veterans. MRI, MRS, and SPECT brain scan studies showed persistent abnormalities in basal ganglia, brain stem, hippocampus, white matter volume, and cerebral blood perfusion that distinguish symptomatic from healthy veterans. [*Gulf War Illness and the Health of Gulf War Veterans, Scientific Findings and Recommendations (PDF), US Department of Veterans Affairs, 2008, p. 222 (p. 232 in PDF), archived (PDF) from the original on 2014-06-03.*]

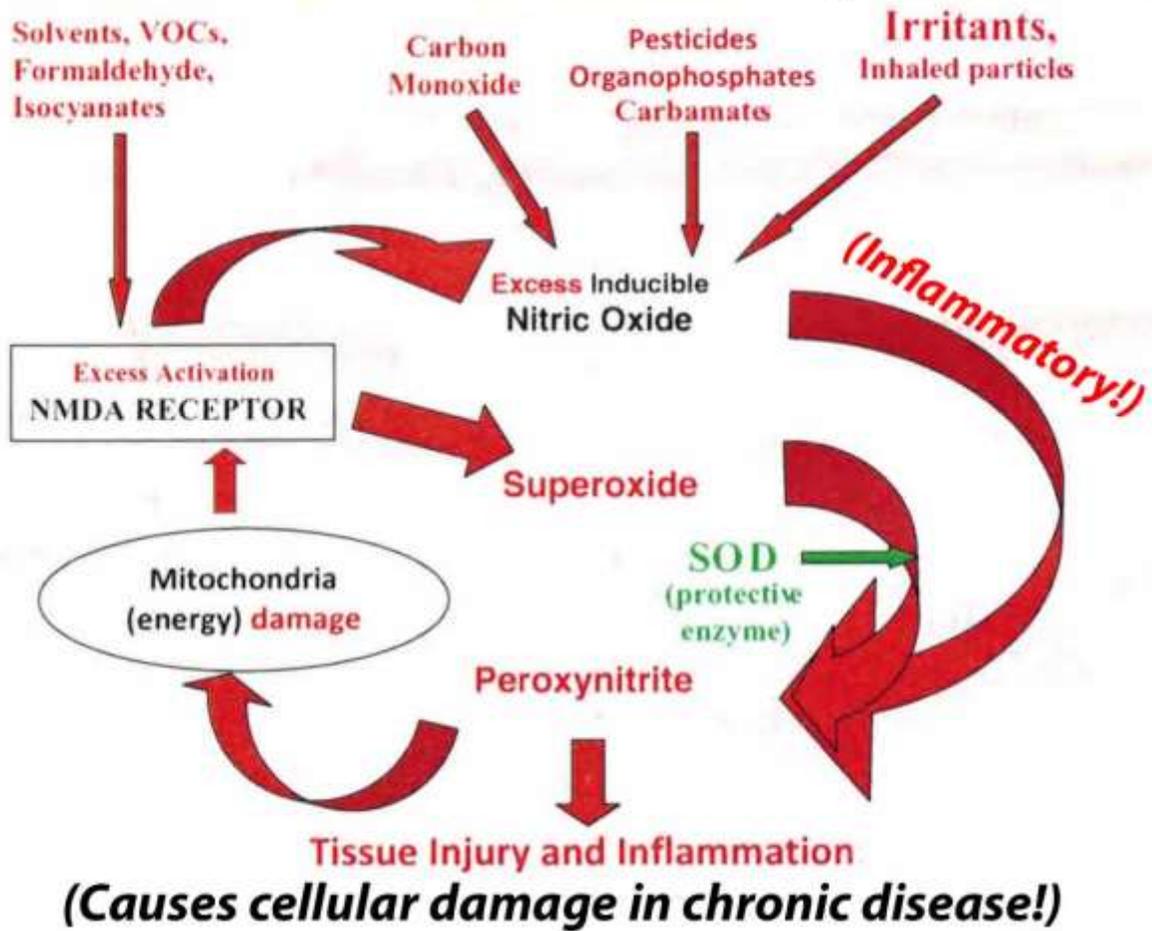
The commonly used MMPI psychological test is a misleading and inappropriate MCS screening test because it automatically scores physical symptoms as psychological (Davidoff AL et al, *Arch Environ Health.* 2000 May-Jun;55(3):165-75.). (Every serious physical illness, especially if chronic, causes associated psychological stress. Don't confuse emotional reactions with causes.)

Conclusion:

An illness cannot be psychogenic when it is correlated with a combination of exposure-triggers, documented biochemical and structural changes (if the right tests are used), and genetic risk

factors. These complex biomolecular abnormalities cannot be documented by common traditional lab tests, or seen or heard or palpated on a physical exam, which would be misleading if relied upon for diagnosis. It's important to look in the right places as documented above; otherwise, absence of evidence of the diagnosis, by not seeing it, is not evidence of absence.

INFLAMMATION: A Vicious Cycle!



("Vicious Cycle" diagram from "The Toxicant Induction of Irritant Asthma, Rhinitis, and Related Conditions", WJ Meggs, Ed, © Springer Science+Business Media, LLC, 2013, P 251.)