Neural Sensitization and Multiple Chemical Sensitivity

by

Mark J Donohue

Introduction

“Specifically, individuals with high Chemical Intolerance (CI) have a heightened susceptibility to neurohormonal sensitization. The neurohormonal sensitization model for low-level chemical intolerance proposes (1) the involvement of the olfactory-limbic and mesolimbic pathways in the brain and (2) in this model, the heightened central nervous system reactivity leads to dysfunction of regulatory pathways for the autonomic, endocrine, and immune systems as well as of cognition and affect. In turn, these dysregulations help generate the polysymptomatic clinical pictures of patients with Chemical Intolerance.” (Bell – 10)

In the first couple of reports we learned, despite the claims of the critics, that there is plenty of evidence in the scientific literature proving that multiple chemical sensitivity (MCS) is a real physiological disorder. We also learned that those who suffer from MCS are known to have a long list of symptoms which are usually triggered by an even longer list of chemicals, foods, and drugs. Sadly, we also learned through several prevalence studies that 11.2 – 16% of the American population are hypersensitive to chemicals. Of which 2.5 – 3.1% have actually been diagnosed with MCS. These figures also contradict the claims by critics - that accounts of MCS are rare isolated incidences. Finally, for those who did not have a background in the medical sciences, we learned, some basic anatomical structures and neurophysiology involved in the human nervous system. With this foundational information, it is now time to learn about the various biochemical mechanisms which may be involved in the development of MCS.

MCS Research

“There are two primary schools of thought or fundamental theories that drive and divide MCS researchers: (1) MCS is a psychogenic condition and (2) MCS is an organic condition.” (Miller – 19)

Psychogenic condition – refers to a disorder that often results from mental or emotional conflicts where an anatomical abnormality has not been found. Or more simply put - a condition caused by psychological factors, particularly psychological stress, trauma and/or anxiety. Obviously, these are important factors in the study of MCS, as they are in all illnesses. However, the psychogenic component will not be covered in this report; rather it will be covered at a later time after all the physiological and biochemical possibilities have first been covered.
With that said one should take note of the quote from “Miller”:

“It has been hypothesize that certain cases of depression and somatoform disorders (psychogenic) may be caused or exacerbated by chemical exposures and thus could share the same biochemical underpinnings as MCS.” (Miller – 20)

Point being - instead of psychological factors being the cause of MCS, maybe MCS and psychogenic disorders share the same physiological and biochemical pathways. And thus, maybe, MCS and psychogenic disorders are on a continuum with each other. On the low end of the continuum, low-level exposures to certain chemicals will cause depression and anxiety in susceptible individuals while on the high end of the continuum, after either an acute high-level or chronic low-level exposure to certain chemicals, MCS will develop in susceptible individuals.

**Organic condition** - refers to a disorder that has a real anatomical, physiological, or biochemical component to it. MCS is such a condition, and in my report – “The Physiological Basis for Multiple Chemical Sensitivity” – I list several studies proving this point.

“The most frequently cited physiological theories to explain chemical sensitivity involve the nervous system, the immune system, or the interaction between them because these two systems most dearly link the external environment and the internal milieu. The rapid responsiveness of these systems also makes them attractive candidates because symptoms of food or chemical sensitivity have been reported to develop within seconds of exposure.” … and it has been “proposed that the human nervous system, because it is so highly evolved, may be most susceptible to environmental agents.” (Ashford - 18)

Another compelling argument for MCS as an organic condition is that researchers have identified MCS occurring among demographically diverse groups in more than a dozen countries - nine European countries, the U.S., Canada, Japan, Australia and New Zealand. Some of these demographically diverse groups include:

- United States - EPA (Environmental Protection Agency) employees in Washington, DC, exposed to volatile organic chemicals *out gassing* from new carpet, paint and construction materials.
- United States - Card dealers in a Lake Tahoe (California) casino exposed to solvents and pesticides.
- Canada - Hospital workers in Nova Scotia exposed to building air contaminants.
- Great Britain - Sheep dippers were exposed to organophosphate pesticides.
- New Zealand - Radiology workers were exposed to X-ray developer solutions containing glutaraldehyde.
- Germany - Families in Germany exposed to pentachlorophenol wood preservative in their log homes.
- Iraq - Gulf War veterans exposed to solvents, combustion products, pesticides and various drugs.
“That people from such diverse groups—different occupations, different socio-economic classes, even different cultures—report developing multisystem symptoms and new-onset intolerances following a chemical exposure event is notable, but the fact that they also report new-onset intolerances for alcoholic and caffeinated beverages, medications, and foods—not just chemical inhalants—is a compelling anomaly. In science, compelling anomalies expose the limitations of existing paradigms and drive the search for new ones.” (Miller – 22)

Phases of MCS

Regardless of a persons’ socio-economic class or home country, MCS has been described as a dual phase process. The first stage involves sensitization to an initial chemical exposure, and is sometimes referred to as initiation or the initiation phase. The second stage involves the triggering of reactions upon further chemical exposures, and is sometimes referred to as elicitation or the elicitation phase.

Prior to the development of MCS, a person generally lead a normal life and remained asymptomatic until the occurrence of the sensitizing event. The sensitizing event can be either a single high-level exposure (i.e. chemical spill), or the sensitizing event could be repeated long term low-level exposures (i.e. working or living in a newly renovated building or home). Individuals who develop MCS may be initially susceptible due to genetics, imbalanced hormones, poor nutrition, environmental factors or stress.

“MCS appears to evolve in two stages: (1) initiation, characterized by a profound breakdown in prior, natural tolerance resulting from either acute or chronic exposure to chemicals (pesticides, solvents, indoor air contaminants, etc.), followed by (2) triggering of symptoms by small quantities of previously tolerated chemicals (traffic exhaust, fragrances, gasoline), foods, drugs, and food/drug combinations (alcohol, caffeine).” (Miller – 23)

An interesting distinction between the two phases is that the number of chemicals that trigger reactions far out weights the number of chemicals that initiated MCS.

“The number of chemicals that appears to initiate MCS, while diverse, is not as widely varied as the number of chemicals that triggers symptoms in chemically sensitive individuals.” (Sorg – 28)

While many environmental chemicals have been shown to initiate sensitization (flame retardants, formaldehyde, benzene, ozone, etc.), the number one culprit is pesticides.

“Various pesticides have already been shown to induce sensitization.” (Bell – 3)
“Many environmental chemicals, especially pesticides induce chemical kindling or partial kindling, or facilitate electrical kindling (types of sensitization) of the amygdala in animals.” (Bell – 8)

The fact that pesticides are the number one substance shown to initiate sensitization and trigger reactive states is not surprising to those with MCS. Nor is it surprising to hear about most of the many other chemicals involved in the initiation phase of sensitization (See Table 1). However, there are a few that might surprise people, two that surprised me are:

(1) **Opioid activating foods**

“Cacosmia (increased sensitivity to odors) correlated significantly with self-reported illness from foods - wheat, dairy, eggs - that may mobilize or generate opioid peptides.” (Bell –3)

“Opioid peptides also act on the brain to induce both limbic kindling and TDS (sensitization) of behavior in animals.” (Bell –3)

(2) **Low testosterone**

“It has been shown that removal of the gonads in younger male animals increases their vulnerability to TDS (sensitization).” (Bell -12)

“Female animals are more vulnerable than are males to TDS (sensitization); estradiol accelerates the process of sensitization.” (Bell – 13)

**Table – 1: Agents proven to initiate neurobehavioral sensitization in lab animals (Bell – 10)**

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<thead>
<tr>
<th><strong>Endogenous Mediators</strong></th>
<th><strong>Drugs</strong></th>
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<tr>
<td>Interleukin</td>
<td>Ethanol</td>
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<td>Substance P agonist</td>
<td>Carbachol</td>
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<tr>
<td>Enkephalin</td>
<td>Physostigmine (cholinomimetics)</td>
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<tr>
<td>Beta-endorphin (m-opioids)</td>
<td>Morphine</td>
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<tr>
<td>Corticosterone</td>
<td>Amphetamine</td>
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<td>Estrogen</td>
<td>Cocaine</td>
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<td>Neurotensin</td>
<td>Antidepressants</td>
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<td>Haloperidol</td>
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<td></td>
<td>Diazepam</td>
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<td></td>
<td>Inverse benzodiazepine agonist</td>
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<tr>
<td></td>
<td>Clonidine</td>
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<td>2-Deoxy-D-glucose</td>
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<tr>
<th><strong>Environmental Chemicals</strong></th>
<th><strong>Physical Stressors</strong></th>
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<tr>
<td>Formaldehyde</td>
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<td>Toluene</td>
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<td>Chlorinated hydrocarbon pesticides</td>
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<td>Organophosphates</td>
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<td>Mint</td>
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<th><strong>Psychological Stressors</strong></th>
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Roughly half of those who develop MCS say it began following a specific exposure, for example exposure to: a chemical spill, a pesticide application, etc... The other half who develop MCS have no recollection of any type of acute exposure, but most likely developed MCS through a chronic low-level exposure.

“60% of MCS cases report an identifiable chemical initiating event... in addition, approximately 40% of MCS patients cannot identify a specific initiating chemical exposure event.” (Bell – 7)

There may be another reason why 40% of those with MCS have no recollection of any type of exposure... acute or chronic low-level. It is not always the case that a sensitizing event is due to a chemical exposure. Initiation and sensitization can also occur from intense physical stressors or even highly emotional traumatic events. In other words – stress!

“Cortisol (stress hormone) and related hormones may be key participants in sensitization. Adrenalectomy (removal of adrenal gland) can prevent the induction of sensitization in animal studies.” (Bell – 6)

“One of the most reliable behavioral indicators of elevated sensitizability is hyper-reactivity to novelty. Animals who show spontaneously high rates of activity when placed in a novel physical environment later sensitize more strongly to drugs.” (Bell – 6)

“The ability of a wide variety of chemically dissimilar drugs to induce TDS (sensitization) suggests that it is the stressful or foreign properties of the drugs, rather than their pharmacological actions, that initiate TDS.” (Antelman - 1)

Masking and Spreading

What takes place after a person reaches the breaking point of chemical intolerance (CI), whether from an acute or chronic exposure, is usually the same. A person will first develop “flu-like” symptoms that just won’t go away. Or maybe they will feel they are in a perpetual “brain fog”. Soon afterwards the person will develop more and more symptoms which will unpredictably wax and wane. All the while the person is unaware as to the cause of all their new symptoms and so too are physicians. This delay in the recognition, between exposure and symptoms, is usually due to a concept called “masking”.

“Masking” (acclimatization, apposition, and addiction) may hide these exposure-symptom relationships, thus obfuscating the environmental etiology of the illness.” (Miller – 20)
“Many patients, perhaps the majority, are not even aware they have intolerances, due to a phenomenon called “masking”. Masking tends to hide the relationship between an individual’s symptoms and triggering exposures. It has several interactive components. One masking component, apposition, occurs when people become intolerant to many different substances. As these individuals go through the day multiple symptoms, triggered by fragrances, hair spray, vehicle exhaust, foods, medications, etc. overlap, creating a confusing array of symptoms. No one cause can be isolated because there is too much background noise. Addiction to caffeine, nicotine, or alcohol can also mask the effects of chemical inhalant exposures. People exposed to the same substance more than once every 4–7 days tend to habituate to that substance. Habituation also masks responses. Masking helps explain why symptoms vary from person to person, and from day to day in the same individual.” (Miller – 22)

At some point, maybe on the advice of a physician or maybe on their own experimentation, a person will start to suspect something in their environment or in the food they are eating as a possible cause to their problems. This is when the associations are made and when a person will start to “avoid” certain environments and foods. “Unmasking” will now begin along with the realization of what has been causing many of their symptoms.

“Many MCS patients say that when they first became ill, they had no idea chemical exposures had anything to do with their symptoms. They say it was not until they avoided (accidentally or intentionally) a sufficient number of their problem initiants simultaneously that they noticed feeling better. Then, when they reencountered something to which they were sensitive, their symptoms recurred.” (Miller – 20)

Unfortunately, it maybe, the more a person unmasks the more they become aware of new intolerances. Over time the number of intolerances grows to include a wide variety of everyday chemicals, foods and drugs, which are completely unrelated. This has been termed the “spreading phenomenon” and the term “universal reactor” has been coined to identify such persons with a long list of intolerances.

“Once the syndrome has been initiated, a “spreading phenomenon” reportedly occurs, in which sensitivity generalizes from the original agent to low doses of multiple, chemically unrelated substances.” (Bell – 2)

It also needs to be noted that the spreading phenomenon is not restricted to just chemicals and foods. It is common for a person with MCS, especially the more severe universal reactors, to also be highly sensitive to sounds, bright lights and even touch. This is another indication that the entire central nervous system is involved in this disorder and why it affects nearly every organ system.

“MCS patients often acknowledge hyper-reactivity in various other sensory modalities, including noise, light and touch.” (Bell – 4)
“MCS patients show that they consider themselves to have more acute sensory function in smell, taste, and hearing... The limbic structure of the amygdale is part of the olfactory pathways. The central nucleus of the amygdale is also one of several brain regions that modulate startle reactions to unexpected noise... As a result, individuals who are sensitive to both chemicals and noise might be among those most vulnerable to limbic dysfunction and to sensitization of limbic and other central nervous system responses by multiple environmental factors.” (Bell – 5)

**MCS and the CNS**

It should be apparent by now that the consensus among many of the MCS researchers is that the main organ system involved in multiple chemical sensitivity (MCS) is the nervous system, specifically the central nervous system (CNS). What you should also be apparent by now is that the **limbic system** consisting of the - olfactory bulb, amygdale, hippocampus, thalamus and hypothalamus - are the main structures most affect in those with MCS.

“A potentially promising line of animal research relevant to multiple chemical sensitivity (MCS) is that of sensitization in the central nervous system (CNS), particularly limbic pathways in the brain.” (Sorg – 25)

“Most studies implicate changes occurring within the CNS in the majority of MCS patients. Regardless of whether the origin of MCS is "biogenic" or "psychogenic", CNS circuitry is likely to be altered in MCS. Many of the chemicals that have been attributed to triggering symptoms in MCS patients are solvents and pesticides, whose primary effects are on the CNS, and are neuro-toxicants when present in higher concentrations.” (Sorg – 28)

“Many environmental chemicals gain access to the central nervous system via the olfactory and limbic pathways, induce lasting changes in the limbic neuronal activity and overall cortical arousal levels and thereby alter a broad spectrum of behavioral and physiological functions to produce clinical MCS syndromes.”(Bell – 2)

“It has been proposed that a key regulatory site for MCS is the brain, specifically the olfactory-limbic and related pathways.” (Bell – 7)

The hypothalamus is the focal point in the brain where the nervous, endocrine and immune system intersect and interact. And it is the olfactory system (bulb, cortex, etc.), via its neural circuitry, that directly links the outside world to the limbic system and hypothalamus. Strong odors and even milder ones, detected by the olfactory system, generate electrical activity in the amygdala and hippocampus which are then projected to the hypothalamus.
“Rich neural connections lie between the olfactory system and the limbic and temporal regions of the brain.” (Ashford – 18)

“Accordingly, olfactory pathways and specifically the olfactory bulbs are particularly sensitive to electrical and chemical kindling (sensitization). The receptors in the olfactory epithelium form a direct access pathway to olfactory structures in the CNS. It is reasonable, therefore to assume that strong activation of the olfactory epithelium cells could provide sufficient input to central olfactory circuits to cause sensitization.” (Rossi – 24)

The hypothalamus not only receives input from the other limbic structures, but also from the cortex. Because of this connection it is important to realize that strong emotions can also trigger hypothalamic responses and create physical effects associated with intense anger and rage, sometimes referred to as hypothalamic rage.

“One intriguing aspect of the limbic system as a mechanism for multiple chemical sensitivities is the system's responsiveness to both chemical and cortical stimuli. Therefore, conscious thought processes and emotional states influence limbic activity just as chemical or physical stimuli can.... Therefore, conscious thought processes could alter some electrical activity in the limbic system.” (Ashford - 18)

Bullectomy (removal of olfactory bulb) in animals results in sensitization of the amygdale. The amygdale is involved in odor analysis and in the regulation of emotions, especially fear and anxiety. Therefore, it is reasonable to think a person with a dysfunctional olfactory system might be predisposed to developing MCS.

“Subsensory exposure to chemicals can cause protracted, if not permanent, alterations in the electrical activity of the limbic region, beginning first with the most sensitive structures, particularly that portion of the amygdala that analyzes odors. “ (Ashford - 18)

The hippocampus is an extremely important structure in learning as well as in the making and storage of memories. Damage to the hippocampus or lesions in this structure will affect a persons’ ability to learn and in their ability to retain and recall memories.

“Learning and memory decrements are a frequent consequence of exposure to toxic substances, and some researchers view the hippocampus as a prime target for such toxins... Remarkably small perturbations of hippocampal function may have large and long-lasting effects upon behavior and cognition.” (Ashford - 18)

As you may also recall, several limbic structures do not have a protective blood brain barrier – hypothalamus, pineal gland, etc... This maybe one of the main reasons the limbic system is sensitive to overstimulation. And it has also been discovered that the olfactory system shares this unique distinction making the limbic system even more vulnerable.
“Among the sensory systems, only the olfactory system lacks a blood-brain barrier. The olfactory bulb, amygdala, and hippocampus are interconnected parts of a phylogenetically older portion of the brain that is particularly vulnerable to sensitization processes. Repeated intermittent exposures to a given stimulus lead to progressively increased levels of responsivity over time in those structures.” (Bell – 8)

“The olfactory cortex handles the sense of smell and is important to emotions and sexual behavior. It has no blood brain barrier, so odorants can easily produce brain damage.” (Erwin – 32)

Neural Sensitization

In the late ‘80s and early ‘90s MCS researchers developed the neural sensitization model for MCS. Neural sensitization is based on previous lab experiments done on animals, which are referred to as animal models. However, these lab experiments were done to study other medical disorders (addiction, seizure disorders, etc.) and not MCS. It wasn’t until the early MCS researchers noticed the similarities between the developed symptoms in animals, after experimentation, and the symptoms in humans with MCS. The models for MCS, therefore, are animal models that were originally developed in other areas of medical research and MCS researchers simply adopted them.

“They have noted that chemical sensitivity strongly resembles the phenomenon of sensitization in rodents observed after repeated exposure to psychostimulants or stress.” (Sorg – 27)

“Sensitization is a type of learning and typically is studied in laboratory animals. The repeated stimuli used to induce sensitization commonly include drugs of abuse, especially psychostimulants such as cocaine and amphetamine.” (Sorg – 28)

The term “neural sensitization” simply refers to neural pathways which become hypersensitive - more easily stimulated or more easily to fire. Neural sensitization is the result of nerve pathways being over stimulated due to a variety of factors such as chemicals, drugs, emotional stressors, etc...

“Sensitization in the neuroscience and pharmacology literatures is defined as progressive increase in the size of a response over repeated presentations of a stimulus.” (Bell – 7, 9)

“Sensitization is the amplification of behavioral and underlying neurochemical responses to a stimulus after repeated perturbation with either stressful stimuli or drugs of abuse such as amphetamine, cocaine, and morphine.” (Sorg – 30)
Because neural sensitization can occur in several branches of the nervous system simultaneously this helps to explain the long list of multi-organ system symptoms in those with MCS.

“Within the different branches of the nervous system, for example, central nervous system (CNS) sensitization can lead to cravings for certain exogenous substances such as foods; autonomic nervous system (ANS) sensitization can lead to progressive increases in heart rate, blood pressure, visceral contractions, sweating response, or pupillary response; and peripheral nervous system (PNS) sensitization can lead to progressive increases in muscle tension with resultant chronic pain.” (Bell – 12)

Either way, once a person has become sensitized subsequent elicitation or triggering of reactions can now involve low or non-toxic levels. In layman’s terms – “once you cross the line…. “ This author refers to the day I crossed the line as - “the day I broke”.

“Then something happened, though I’m not sure what, and I began to develop an array of health problems. Though I was slowly coming to the realization that something was starting to go wrong with me, I still had plenty of energy and had no interest in seeing doctors. ... Then came the day I crossed the line and broke. I remember “the day I broke” vividly, I was thirty-five, and one afternoon I was sitting in a Lazy Boy chair napping. When I woke up, I quickly realized something was wrong. I had no energy, none! Eventually, I got the strength to get up from the chair, but within a couple of hours I was developing classic flu-like symptoms.” (Johnson – 17)

**Amplification**

Amplification is at the core of the neural sensitization model and in the development of MCS. In the context of MCS, amplification means to boost or increase the original nerve impulse which in turn causes the neuron to become hypersensitive... too easily and/or continually fire.

“Recent and ongoing studies in our laboratory have focused on developing an animal model for MCS that is based upon the hypothesis that repeated chemical exposure produces amplification of central nervous system (CNS) circuitry that underlies changes in behavior and symptoms in MCS.” (Sorg – 29)

“Neural sensitization is the progressive amplification of responsivity by the passage of time between repeated, intermittent exposures.” (Bell – 8, 11, 12)

“One site for this amplification may be the limbic system of the brain, which receives input from the olfactory pathways and sends efferents to the hypothalamus.” (Bell – 10)
The phenomenon of amplification is at the heart of the MCS controversy. We know that when most people are exposed to non-toxic levels of chemicals there are no ill effects. Yet in the chemically sensitive, the same exposure will cause the triggering of a reactive state. The end result in the first scenario is... nothing, no ill effect, while in the second scenario... neural sensitization is said to have taken place and the diagnosis is MCS. The difference between these two scenarios is that of amplification of the original nerve impulse.

“The controversy surrounding MCS partly stems from the question of how amplification of sensitivity to chemicals can occur, since symptoms have been reported after exposure to extremely low levels of chemicals that do not affect the general population.” (Sorg – 25)

“What has confounded toxicologists and allergists, causing some to discount these patients’ claims altogether, are several things. First, the exposure levels or doses said to be causing symptoms are orders of magnitude below established safety limits, leading some scientists to dismiss the illness entirely, on the basis that it violates a fundamental tenet of toxicology—evidence of a dose—response relationship.” (Miller – 22)

Types of Neural Sensitization

To this point several types of neural sensitizations have been mentioned in this report without further explanation. This is due to the fact that in reading over two dozen medical studies and books on MCS, I found no explanation or clarification to the confusing terminology and definitions behind the different types of neural sensitization and how they relate to each other, if at all. This was extremely frustrating and time consuming to say the least. Luckily ‘Rossi’ did a review of the MCS literature and was able to give some organizational sense to it all. So below is a list of the different types of neural sensitization with a brief description (though somewhat technical).

“An olfactory-limbic model for the MCS syndrome was initially proposed by Bell (1992)...The initial model proposed that some combination of direct olfactory stimulation (e.g. Bokina et al., 1976), systemic chemical kindling (e.g. Mason and Cooper, 1972; Post et al., 1975; Post and Kopanda, 1976), partial kindling (e.g. Adamec and Stark-Adamec, 1983) and time dependent sensitization (e.g. Antelman, 1988) could account for the initiation, amplification and persistence stages of the MCS.” (Rossi – 24)

Types of neural sensitization:

- **Long-Term Sensitization (LTS)** – “refers to the processes underlying changes from baseline of some physiological or behavioral endpoint that are reflected shortly after the sensitizing event and which persist for an indefinite period of time.” (Rossi – 24)
➢ **Time-Dependent Sensitization (TDS)** – “refers to the ability of mild stressors – whether pharmacological or environmental – to induce physiological and behavioral effects which then progress, i.e. get stronger, entirely as a function of the passage of time since stressor presentation. This strengthening is revealed when the organism is later exposed to either the original or another stressor.” (Antelman – 1)

➢ **Learning** – “as described in most introductory psychology textbooks as a relatively permanent change in behavior brought about by experience, clearly represents the most ubiquitous form of sensitization.” (Rossi – 24)

➢ **Kindling** – “is the ability of an initially subthreshold stimulus without convulsant properties to elicit a tonic-clonic seizure on subsequent reexposure following repeated intermittent exposures to the stimulus. Kindling appears to be permanent, or at least long-term.” (Bell – 4)

- **Electrical Kindling** – “refers to the induction of generalized epileptic seizures following repeated electrical stimulation of brain tissue at levels initially insufficient to induce motor convulsions.” (Rossi – 24)

- **Partial Kindling** – “Unlike the classical electrical kindling paradigm, however, partial kindling is discontinued before the elicitation of generalized motor seizures. The dependent variables in partial kindling experiments are a change in some behavioral endpoint and the persistence of the change.” (Rossi – 24).

- **Chemical Kindling** – “refers to progressive induction of generalized motor seizures following repeated administration of chemical compounds at dose levels initially insufficient to induce motor convulsions.” (Rossi – 24)

  - **Intracerebral-localized (ICL) chemical kindling** - “a convulsant, neurotransmitter, or receptor agonist or antagonist is administered directly to brain tissue through a narrow diameter cannula. The kindling agent is infused periodically, generally at a frequency of once per day. The infused stimulus must elicit localized epileptiform afterdischarges. Subsequent infusions increase the duration of the afterdischarge and lead to recruitment of brain regions more distal to the infusion site. A gradual progression to generalized motor seizures is observed.” (Rossi – 24)

  - **Intracerebroventricular (ICV) chemical kindling** – “ICV chemical kindling differs from ICL chemical kindling in that the kindling compounds are infused into the cerebral ventricles and achieve a much broader dispersion. “ (Rossi – 24)

  - **Systemic chemical kindling** – “refers to a gradual progression to generalized motor seizures observed after spaced, repeated intraperitoneal (i.p.), intravenous or subcutaneous administrations of a chemical compound.” (Rossi – 24)
Mechanisms of Neural Sensitization

At this point we are left with more questions than answers. One of the key questions being - what are the physiological and biochemical mechanisms involved in neural sensitization? This is the question everyone involved in MCS is asking. Unfortunately, researchers have very few answers.

“Unfortunately, the ambiguities surrounding the nature of the relationships between the underlying mechanisms of kindling and related neural sensitization phenomena make it nearly impossible to speculate about which specific underlying mechanisms might be involved in the development of MCS.” (Rossi – 24)

“The mechanisms of sensitization are not fully understood but may involve persistent changes in neurotransmitters, receptors, and basic neural cellular functions.” (Bell – 9)

“The pathophysiology - physiological processes associated with disease or injury - of MCS is not well understood. Various investigators have proposed a range of mechanisms, none of which by itself explains the entire clinical presentation.” (Bell – 15)

Along with my frustration over the lack of clarification about the different models of neural sensitization, I am equally frustrated by the lack of information about the possible mechanisms for the neural sensitization model. I feel somewhat justified in saying this because ‘Rossi’ in his review of the medical literature also appeared to share the same view point.

“The specific mechanisms that might be involved, however, are alluded to only allegorically in terms of TDS, partial kindling and kindling-related phenomena. In order to develop a comprehensive model useful in the study of MCS and related disorders, it is necessary to elaborate on the specific nature of the neural sensitization mechanism(s) that might be involved.” (Rossi – 24)

Despite the lack of any detailed information about possible mechanisms for the neural sensitization model there were, however, several mechanisms that are briefly mentioned or eluded to in the scientific literature. The mechanisms briefly mentioned will serve as a good starting point for further research. Below is a list of possible physiological and biochemical mechanisms involved in the development of neural sensitization, which need further research.

(1) **Olfactory- Limbic System** - despite the lack of conclusive evidence implicating a specific physiological and biochemical mechanism for neural sensitization, what cannot be denied is the predominate role of the anatomical structures involved, namely the structures of the limbic system. Because of this and because it was just learned that the olfactory system lacks the protection of the blood brain barrier, additional research needs to be done on the olfactory – limbic system (see next report).
The Trigeminal Nerve - is the fifth cranial nerve and is primarily a sensory nerve responsible for sensation in the face.

“Detection of chemical stimuli in the nose is not limited to the olfactory nerve, but involves the trigeminal nerve and its afferents which may also play a role in this condition. Trigeminal free nerve endings in the nose and mouth detect noxious chemicals and reflexively initiate protective responses including cessation of breathing, constriction or dilatation of the airways, reduction in heart rate and cardiac output, constriction of most blood vessels (except capillaries in the head), increased epinephrine release, changes in blood pressure and efforts to withdraw.” (Ashford - 18)

(2) Excitotoxicity – is the overstimulation of neurons, especially in the hypothalamus, via the excitatory amino acid neurotransmitter glutamate and the NMDA receptor. This too is a model that has been adopted from medical studies on neurodegenerative disorders such as - Parkinson’s, Alzheimer’s, Huntington’s disease, etc.

“Additional studies suggest that one potential overlap between cocaine sensitization, cocaine-kindling, and electrical kindling occurs at the N-methyl-d-aspartate (NMDA) glutamate receptor subtype.” (Sorg – 26)

Specifically, the prefrontal cortex shows enhanced excitatory amino acid activity as part of the long-term neurochemical changes during elicited sensitized reactions.” (Bell – 10)

“Sensitization appears to involve excitatory amino acids, essential neurotransmitters present in central nervous system pathways involving pain reception, olfaction, learning and memory.” (Miller – 19)

Excitation of the Mesolimbic Dopamine Pathway - the mesolimbic dopamine system are pathways in the brain in which dopamine (neurotransmitter) is carried from one area of the brain to another. Dopamine is responsible for controlling the brain’s pleasure and reward centers. The structures of the brain that interconnected in this pathway are the midbrain’s ventral tegmental area, the medial prefrontal cortex, and the limbic system.

“Some of our recent blood findings support a possible role for increased dopamine receptor sites (e.g. type D2), heightened receptor responsivity, and/or increased dopaminergic activity in chemical sensitivity.” (Bell – 7)

“The mesolimbic dopaminergic [reward] pathways in the brain (e.g., from the ventral tegmental area to nucleus accumbens) are implicated in sensitization.” (Bell – 10)
“...sensitization involves multiple neurotransmitters, notably dopamine in the mesolimbic pathway... and limbic structures.” (Bell – 11)

“Initiation events are thought to take place within the midbrain dopaminergic neurons in the ventral tegmental area (VTA).” (Sorg – 28)

(5) **Stimulation of Opioidergic Neurons by Opioid Activating Foods** - mentioned earlier, opioidergic neurons are highly concentrated in the ventral tegmental area, which is part of the mesolimbic dopamine pathway.

“The present data on greater intolerance of opiate drugs and opioid-activating foods suggest endogenous opioids can be at least one unifying agent for apparent cross-sensitization to multiple substances.” (Bell – 3)

(6) **Hormonal Imbalances**, - also mentioned earlier, hormone production is the main task of the endocrine system which is controlled by the hypothalamus.

“In animals, higher estrogen: progesterone ratios facilitate neural sensitization, while higher testosterone levels inhibit neural sensitization... the data consistently show that persons with CI (chemical intolerance), in both clinical and nonclinical samples, are primarily women (70–80%).” (Bell – 12)

“Animal researchers have shown that one administration of corticotrophin-releasing hormone (CRH) induces kindling-like changes in limbic firing activity.” (Bell – 3)

“Higher initial levels of corticosterone in animals predict drug sensitization.” (Bell – 6)

(7) **Decreased Acetylcholinesterase (AChE) Activity**. - AChE is an enzyme found in neuron synapses whose purpose is to break down acetylcholine (neurotransmitter) after it has stimulated the neuron. Absence of this enzyme will cause a build up in the synapse and has been implicated in the cause of Gulf War Syndrome. The area of the body which is rich with these enzymes is none other than the limbic system. Pesticides work by blocking AChE.

“The AChE may play a protective role by enzymatically maintaining acetylcholine concentrations at nerve junctions within safe bounds and protecting susceptible cells in the limbic system from developing "bizarre sensitivity". Interestingly, physicians who treat patients with multiple chemical sensitivities have noted some of the most severe and debilitating exposures for these patients have involved organophosphate pesticides, which inhibit AChE.” (Ashford – 18)
Conclusion

Despite being left with more questions than answers there are several working points for future MCS research: (1) The central nervous system (CNS) is strongly implicated in multiple chemical sensitivity (MCS). (2) Animal studies have shown that neurological pathways can be highly sensitized, thereby giving rise to the model of – neural sensitization in those with MCS. (3) The neurological pathways most susceptible to sensitization involve the olfactory, limbic and mesolimbic systems. (4) The concept of nerve impulse amplification has been proposed as the differentiating factor between non-reactive individuals and those highly reactive individuals with MCS. (5) There are several possible biochemical mechanisms that have been proposed to be involved in MCS, which also need further research.

References

**Seymour M. Antelman Ph.D.**


**Iris R. Bell, M.D., Ph.D.**


 Differences in Neural Sensitization and the Role of Context in Illness from Low-level Environmental Chemical Exposures, 

 Sensitization and Kindling Hypothesis for Illness from Low Levels of Environmental Chemicals, *Environmental Health 


11. Bell I.R., Baldwin C.M., Fernandez M., Schwartz G.E., Neural Sensitization Model for Multiple Chemical Sensitivity:


System Model, *Multiple Chemical Sensitivities: Addendum to Biologic Markers in Immunotoxicology*, National Academy 

**Pamela Gibson, Ph.D.**

15. Gibson P.R., What Causes Multiple Chemical Sensitivity, [www.mcsresearch.net](http://www.mcsresearch.net)

16. Gibson, P.R., Elms A.N., Ruding L.A., Perceived Treatment Efficacy for Conventional and Alternative Therapies Reported 

**Alison Johnson, M.S.**


**Nicholas A. Ashford, Ph.D., J.D.**

18. Ashford N., Miller C., Possible Mechanisms for Multiple Chemical Sensitivity: The Limbic System and Others, 
*Multiple Chemical Sensitivities: Addendum to Biologic Markers in Immunotoxicology*, National Academy Press (1992)

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John Rossi III, Ph.D.


Barbara A. Sorg Ph.D.


Herman Staudenmayer Ph.D.


Harry R. Erwin Ph.D.

32. Erwin H.R., The Hippocampus and the Olfactory System – Lecture 12, University of Sunderland