

POSSIBLE MODELS FOR MULTIPLE CHEMICAL SENSITIVITY: CONCEPTUAL ISSUES AND ROLE OF THE LIMBIC SYSTEM

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INTRODUCTION

*It was six men of Hindostan,
To learning much inclined,
Who went to see the elephant,
(Though all of them were blind);
That each by observation,
Might satisfy his mind.*

J. G. Saxe

There is an accumulating number of clinical observations concerning patients who report multiple chemical sensitivities (MCS), and investigators who might propose a mechanism or model to explain this syndrome should be aware of these observations. Some observations have come from researchers, some from clinicians, and some from MCS patients. Few of these observations have been tested in a scientific manner. Nevertheless, taken as a whole, they may provide us with important clues about the MCS "elephant." The purpose for reviewing these observations is 1) to provide a common body of data, anecdotal or otherwise, to facilitate discussion of the problem and thereby 2) to enhance the probability of generating fruitful mechanistic hypotheses. Consider this a kind of brainstorming session—an attempt to write all our ideas on the blackboard while suspending judgment about their correctness or utility. Later we can edit them as we learn more.

Remarkably, despite the lack of an accepted clinical case definition for MCS, most physicians who are aware of this problem almost immediately recognize these patients. This process has a gestalt-like quality. We must find ways to dissect these clinical intuitions, frame them as hypotheses, and test them in a scientific manner.

Persons who have worked with MCS patients can readily attest that getting involved with their medical problems and lifestyle difficulties can be both time-consuming and exceedingly frustrating, for a variety of reasons. Yet MCS may represent an unprecedented opportunity to further our knowledge of environmental health, psychology and psychiatry, or all of these

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(depending upon our personal views of the etiology of this problem). Throughout the history of science, the diligent pursuit of rare, serendipitous events has produced enormous yields. Wilson's cloud chamber allowed physicists to capture rare atomic events, providing new information concerning protons, electrons, and other sub-atomic particles. In medicine, rare genetic events have provided valuable clues about the human genome. The diligent study of MCS patients may also lead us toward unanticipated discoveries.

It is hoped that the following observations (and they are *only* observations) will lead to clearer hypotheses and experiments to test those hypotheses. Science is not about "belief." It is about "guess and test," that is, formulating hypotheses that can then be subjected to scientific scrutiny. Many, if not all, of us have strong personal beliefs about chemical sensitivity. Despite our differing views, we should nevertheless be able to agree on which hypotheses and mechanisms are most plausible and how to test them in an objective manner.

OBSERVATIONS ON MCS

Induction (Priming or Sensitization)

Onset Following a Major Chemical Exposure. In many cases, MCS appears to follow a major exposure to any of a wide range of environmental chemicals. The exposure may occur briefly at high levels or repeatedly or continuously at lower levels. Commonly reported inducing (priming or sensitizing) exposures include pesticides, solvents, or complex mixtures, such as combustion products or indoor air pollutants. However, onset of illness has been attributed to various other events, for example, surgery with anesthesia, pregnancy, extreme stress, or courses of various drugs. In one survey of 6800 persons reporting chemical sensitivities, almost 50% blamed pesticides (National Foundation for the Chemically Hypersensitive, 1989). Between 1984 and 1990, the National Pesticide Telecommunications Network received more than 1000 calls on chemical sensitivity attributed to pesticide exposures (NPTN, 1991). A disproportionate number (relative to exposure opportunity) involved organophosphate pesticides.

Demographic Diversity. MCS-like illnesses have been reported by industrial workers, individuals exposed in contaminated communities, tight-building occupants, and individuals with personal and unique exposure histories, for example to pesticides in their homes (Table 1). These groups differ greatly in terms of age, sex, social group, and the kinds of medical specialists they consult. What they share in common is a history of a major chemical exposure event and similar kinds of complaints following that event, particularly complaints about symptoms occurring after exposure to common environmental substances that were formerly tolerated. The demographic diversity of these groups suggests that a real problem may be occurring.

Temporal Cohesiveness. The temporal cohesiveness of MCS-like illnesses occurring within a group of individuals sharing a recognized, major chemical exposure (for example, near-simultaneous development of symptoms in several family members, co-workers, or

community members exposed to the same chemical or mix of chemicals) helps point to a problem that is real in those circumstances.

TABLE 1. Chemically Sensitive Groups

Group	Nature of Exposure	Demographics
Industrial workers	Acute and chronic exposure to industrial chemicals	Primarily males; blue collar; 20 to 65 years old
Tight-building occupants	Off-gassing from construction materials, office equipment or supplies; tobacco smoke; inadequate ventilation	Females more than males; white collar office workers and professionals; 20 to 65 years old; school children
Contaminated communities	Toxic waste sites; aerial pesticide spraying; ground water contamination; air contamination by nearby industry and other community exposures	All ages, male and female; children or infants may be affected first or most; pregnant women with possible effects on fetuses; middle to lower class
Individuals	Heterogeneous; indoor air (domestic), consumer products, drugs, and pesticides	70-80% females; 30 to 59 years old (Johnson and Rea, 1989); white middle to upper middle class and professionals

Source: Ashford and Miller, 1991.

Total Load. An apparent threshold effect, referred to by some as the patient's "total load," has been noted and cited by some practitioners to help explain why an individual develops this syndrome at a particular time. Illness is said to occur when the total load of biologic, chemical, physical, and psychologic stressors exceeds some threshold for the patient. This concept has emerged from clinical observations. No direct experiments have been done to test its validity in humans. However, Hans Selye's work demonstrating the General Adaptation Syndrome in animals exposed to various stressors lends support to this idea (Selye, 1946).

Triggering

Triggering by Extremely Low Levels of Chemicals. Following induction of the illness, patients report subsequent triggering by extremely low levels of exposure to common chemicals, levels that are tolerated by most of the population.

Spreading. Spreading of sensitivities to other, often chemically dissimilar, substances is commonly reported, with each substance triggering a different but reproducible constellation of symptoms.

Characteristic Constellation. For a given patient with a given exposure, a characteristic constellation of symptoms results. Indeed, even when no odor is present, MCS patients may be able to identify the nature of the exposures based solely upon the pattern of symptoms they experience.

Dose dependence. The severity of symptoms is proportional to the "dose" (duration and magnitude) of the exposure in the sensitized individual.

Pronounced Stimulatory and Withdrawal Symptoms. MCS patients sometimes report that when they are exposed to environmental incitants, either foods or chemicals, they may initially experience a stimulated feeling that is either pleasant (euphoria) or unpleasant (jitteriness); this is followed by withdrawal symptoms (headache, irritability, depression, fatigue) when the exposure is reduced or terminated (Ashford and Miller, 1991). Very sensitive individuals report having experienced fewer and shorter-lived stimulatory effects and more pronounced withdrawal symptoms as their illness progressed. In an extreme case, onset of exposure might be associated with manic behavior and withdrawal from the same exposure might be linked to depression.

Inter-Individual Variability. Different MCS patients exposed to the same substance(s) may experience different symptoms and symptom severity.

Intra-Individual Reproducibility. Individual MCS patients report similar symptoms occurring each time a specific exposure is encountered.

Multiple Exposure Routes Trigger Symptoms. Patients' symptoms may be triggered by inhalation, ingestion, mucosal contact, or injection. Eyedrops, dental materials, suppositories, IVs, and other exposures have been reported to elicit symptoms. Exposure to a given substance in a given patient but via different routes has been reported to result in similar symptoms.

Subsensory Triggering. Onset of symptoms may occur with exposure to chemicals at concentrations below the olfactory threshold. For example, patients may report entering a room, experiencing a "reaction," and learning only later that pesticides had been applied recently. Anosmia and chemical sensitivity are not mutually exclusive; a certain number of MCS patients have no sense of smell, but nevertheless report symptoms with exposure.

Rapid Onset of Symptoms. MCS patients frequently report onset of symptoms within a few seconds of being exposed. In addition, the symptoms have an on/off quality. As quickly as symptoms may begin, an almost immediate cessation of symptoms has been reported following neutralization or use of alkali salts. Such responses might suggest rapid shifts of ions across cell membranes, a neurologic or immunologic mechanism, or possibly conditioning.

Variable Threshold for Triggering. Following development of MCS, major exposures, for example, an airplane trip or exposure to pesticides at work, may result in a general decrease in tolerance for chemical substances, even substances for which tolerance may have been regained. Following such exposures, gradual improvement usually occurs, but it may take days, weeks, or even months, depending on the patient and the severity of the exposure. Patients may say that following a particular exposure, they "lost their foods," meaning they once again lost tolerance for foods they had been able to reintroduce into their diets. This variability in responsiveness in some ways resembles the increased bronchial reactivity that occurs in asthma and increased basophil releasability in atopic dermatitis following major exposures to incriminated inhalants or foods, respectively.

Decrease in Symptoms with Oral Versus Nasal Inhalation. Some MCS patients have noticed that, faced with an unavoidable exposure (for example, traffic exhaust or perfume in an elevator), inhaling via their mouths instead of their noses mitigates symptoms.

Limited Voluntary Control. Certain patients report that biofeedback, self-hypnosis, or variations on these techniques improve their ability to cope during exposures and lessen symptom severity. Such techniques seem to be less helpful for more severe exposures and symptoms.

Adaptation. Adaptation occurs with frequent or continuous exposure, and acute symptoms may become chronic and no longer appear related to particular exposures. This will be discussed later in more detail. Potentially, adaptation may have enormous significance for future research in this area.

Other Intolerances

Food and Alcohol Intolerances. Food and alcohol intolerances are estimated to occur in a sizeable percentage, perhaps up to 80% (Rea, 1988) of individuals with MCS. Foods are complex mixtures of many chemicals, some of which can also be air contaminants. For example, pinene is a constituent of both bathroom air fresheners and oranges. Many MCS patients first become aware of their intolerance for ingestants when they consume an alcoholic beverage, such as red wine or beer, and become ill afterward.

Drug Intolerances. MCS patients often respond poorly to usual doses of medications and may even report difficulties with excipients, binders, coloring, and flavoring agents. Several physicians have reported that their patients are intolerant of the anticholinergic side-effects of various drugs (Schottenfeld, 1987).

Hyperresponsiveness to Physical Stimuli. Some MCS patients may perceive not only chemical but also physical stimuli, including touch, sound, and light, as greatly magnified. These individuals describe their nerves as being easily irritated, and they experience pain or extreme discomfort when someone bumps their bed or they hear conversational-level noises.

Symptoms/Signs

Multisystem Symptoms. Commonly, this patient group experiences symptoms involving virtually any system in the body and often several systems simultaneously. These do not coincide with other known multisystem disorders, such as an endocrinopathy.

Frequent Central Nervous System (CNS) Complaints. Mood, memory, and concentration difficulties are among the CNS symptoms these patients report most frequently.

Rhinitis. The majority of MCS patients appear to have nasal inflammation or rhinitis, suggesting that inflammatory processes are involved in MCS. Rhino-laryngoscopy, nasal biopsies, and assays of mediators in nasal lavage fluid may provide useful data in the future. Doty (1988) reported greater nasal airway resistance among MCS patients than normal controls, both before and after unblinded exposure to phenyl ethyl alcohol and methyl ethyl ketone. Despite increased nasal airway resistance, Doty's subjects had olfactory thresholds for phenyl ethyl alcohol and methyl ethyl ketone that did not differ significantly from the olfactory thresholds of controls.

Personal/Predisposing Characteristics

Apparent Female Preponderance. Among certain demographic groups in which chemical sensitivities have been reported, a greater number of females than males appear to be affected. Although exposure to domestic chemicals in poorly ventilated homes cannot be discounted as a factor, numerous medical conditions and diseases, such as most connective tissue diseases, show a disproportionate number of females affected. Because the maternal immune system is challenged with paternal antigens during pregnancy, its immunologic repertoire and responses may somehow make it more vulnerable to chemical exposure. In a Soviet experiment, females were shown to be more susceptible to the effects of low-level organophosphate exposure than their male counterparts (Krasovskii et al.). The incidence of cutaneous drug reactions in females is 35% greater than among males (Bigby et al., 1986).

Food Cravings and Addiction. Patients often report having carbohydrate or other food cravings, being "chocoholics" or addicted to certain foods, such as baked goods, peanuts, popcorn, sugar (especially corn sugar), potatoes, a particular soft drink, etc. Some report sipping coffee, tea, or soda all day long, carrying it with them wherever they go. Intense food cravings following chemical exposures may be reported, for example, an uncontrollable urge to stop and buy candy after driving in heavy traffic.

Pre-Morbid History of Ill-defined Medical Conditions. Diagnoses such as hypothyroidism, chronic fatigue, temporomandibular joint dysfunction, and fibrositis seem to be more prevalent among MCS patients. Simon et al. (1990) reported an average of 6.2 unexplained physical symptoms before workplace exposure among workers who developed "environmental illness," versus 2.9 such symptoms for controls.

Pre-Morbid History of Depression. Simon et al. (1990) also found that 54% of workers who developed chemical sensitivity reported anxiety or depression prior to their workplace exposure, versus 4% of controls. Others corroborated these impressions, although the sources of these patients' depression and anxiety, whether endogenous or chemically-related, have yet to be demonstrated.

Target Organs Vary Over Time. Patients may report lifelong medical problems, but these affect different organ systems over time. For example, they may have experienced colic as babies, asthma in grade school, stomach problems in high school, headaches in college, and finally chronic fatigue and memory and mood difficulties following a major exposure event.

Family History of Chemical Intolerance. Many patients report a family history of chemical intolerances or addiction. The fact that similarly-exposed co-workers or household members of patients often do not develop MCS suggests that MCS patients have a possible genetic, nutritional, psychologic, or other predisposition, or an accumulation of effects from prior exposures.

Laboratory Findings

Lack of a Consistent Immunologic Abnormality. A variety of immunologic tests have been conducted in this patient group including measures of both cellular immunity (especially T and B lymphocyte counts and ratios) and humoral immunity (especially immunoglobulin levels). Some of the most striking data are those of Levin and Byers (1987), which show an apparent decrease in helper/suppressor ratios among various exposed populations compared with controls. By contrast, other investigators claim that immune parameters for these patients generally fall within expected normal ranges (Terr, 1986). Further studies of T and B lymphocytes in these patients, using healthy age- and sex-matched controls, are needed before conclusions can be drawn. In any event, because helper and suppressor T-cell numbers and ratios of patients and controls overlap greatly, one-time measurements of these parameters are of little value for clinical diagnosis.

Increased Frequency of Autoimmune Antibodies. A few investigators have reported an increased frequency of low titers of various autoimmune antibodies (ANA, anti-smooth antibody, thyroid antibodies, and others) among individuals who report becoming ill after an identifiable exposure to pesticides, solvents, and, more recently, pentachlorophenol (Broughton and Thrasher, 1990; McConnachie and Zahalsky, 1991). One group of researchers has reported that 35 (91%) of 39 individuals with ongoing exposure to trichloroethylene in drinking water had one or more positive results in a panel of autoantibody tests, versus 6 (21%) of 28 controls. Two years after removal from exposure, 41% of the exposure group continued to have one or more positive autoantibody tests, suggesting that avoidance of exposure led to some improvement (Broughton and Thrasher, 1990). The physiologic significance of low titers of autoantibodies is unknown and, although of considerable research interest, their diagnostic utility is compromised because 20% of healthy controls had similar

findings. Such data could suggest an autoimmune response to host proteins altered by reactive environmental chemicals. In future work, careful attention should be directed to employing matched controls and blinded specimens and to assessing inter- and intra-laboratory reproducibility and the day-to-day variation in individual patients' results.

Increased Frequency of Activated T-Lymphocytes. The same laboratories that report an increased frequency of autoimmune antibodies in these patients also report an increased frequency of activated T-lymphocytes (Ta1 or CD26). If borne out, such a finding might suggest an inappropriate or persistent immune response that fails to clear chemicals from the tissues. Activated T cells have been reported in association with multiple sclerosis, infections, and various other inflammatory states. The significance of activated T-cells in this setting is unknown but merits further study.

EEG Abnormalities. A recent study compared EEGs from 58 "universal reactors," 55 healthy controls, and 89 patients from a psychology practice (Staudenmayer and Selner, 1990). EEGs of universal reactors more closely resembled EEGs of psychologic patients than those of controls. The authors, however, dismissed the environmental hypothesis that psychologic and psychiatric disturbances could be consequences, rather than causes, of MCS (Davidoff et al., 1991). Similar EEG changes with increased beta and decreased alpha activity have been reported among organophosphate-exposed workers (Duffy et al., 1979)

ADAPTATION¹

Adaptation is also called "acclimation" or "acclimatization," "habituation," or "developing tolerance." "Acclimatization" often refers to the process of workers gradually becoming accustomed to exposures on the job, for example, heat stress. Understanding the possible role of adaptation in MCS is important for two reasons. (1) Adaptation may interfere with discovering effects on the body from a particular exposure, and (2) chemical exposures may adversely impact adaptative mechanisms and thus lead to illness.

That human beings adapt after chronic exposure to environmental challenges is widely recognized for a variety of substances. For example, the first cigarette an individual smokes might result in eye and throat irritation, but, as they continue to smoke, most individuals adapt over time and experience primarily the pleasurable effects of nicotine on the brain. After months or years, more cigarettes may be required for the same amount of lift, and, eventually, smokers may exhibit addictive behavior, seeking cigarettes more frequently. Subsequent quitting may lead to withdrawal symptoms including irritability, drowsiness, fatigue, moodiness, and headache. The reformed smoker may become extremely intolerant of the smoke of others, even in tiny amounts, and suddenly recall the irritation and unpleasant

¹ Modified in part from Ashford, N.A. and Miller, C.S. (1991). *Chemical Exposures: Low Levels and High Stakes*. Van Nostrand Reinhold, New York.

feelings associated with the first cigarette ever smoked. Over time, the individual had "adapted" to those effects.

Adaptation, which on the surface seems a good thing for the organism, may in fact be a two-edged sword. Tolerance for the noxious properties of exposure may make the individual more comfortable in the exposure and allow other harmful consequences of exposure to continue. Thus, heavy smokers who are "adapted" to tobacco smoke are also at increased risk for developing emphysema, lung cancer, or cardiovascular disease. Parallel analogies are valid for caffeine, alcohol, and other drugs, and frequent exposure may result in adaptation (irritation and other warning signals may disappear), continued exposure may lead to addiction, and reduction or cessation of exposure may precipitate withdrawal symptoms.

Some physicians have observed food and chemical adaptation and addiction in their chemically sensitive patients (Randolph, 1962, 1965). For MCS patients, multiple incitants, not only tobacco smoke, may be involved and, conceivably, all incitants may need be avoided simultaneously for improvement to occur.

Confusion could arise if patients seek physicians' help for withdrawal symptoms when they are no longer exposed (or less exposed) to the offending agents. For example, irritability may occur when individuals smoke fewer cigarettes than usual, or headaches may develop when they drink less caffeine. Such unpleasant withdrawal symptoms may be forestalled by smoking another cigarette or taking another drink of coffee, thus perpetuating addiction. Because smoking a cigarette or drinking a cup of coffee in the morning (after about 8 hours abstinence) relieves irritability or headache and makes patients feel better, they may not suspect that cigarettes or coffee might also be the source of their difficulties.

Occupational health presents other examples of acclimatization, inurement, or tolerance development, for example, after repeated exposure to ozone, nitroglycerin, or solvents (Ashford and Miller, 1991). The incitants mentioned thus far differ considerably from one another; some are ingestants, others inhalants; and their physical states and chemical composition vary greatly. The human body appears able to adapt to an enormous range of substances.

Ozone has been the focus of considerable research on adaptation. Intrigued by how little respiratory illness and death occurred in very polluted cities that had high levels of ozone and suspecting that adaptation might play a protective role, Hackney and associates (1977a) compared the responses of four Canadians (not adapted) and four Californians (adapted) to ozone challenges. Although individual reactivity varied greatly, the Californians were only minimally reactive to levels that caused coughing, substernal discomfort and airway irritation, pulmonary-function-test decrements, and increased red blood cell fragility for the Canadians.

In another experiment, six volunteers with respiratory hyperreactivity were placed in an environmental chamber with ozone at 0.5 ppm, typical of high ambient levels, for four days (Hackney et al., 1977b). Five of six showed decreased pulmonary function during days 1 to 3, but gradually improved almost to baseline by day 4, suggesting adaptation had occurred. The authors note that not all adverse effects of ozone may be prevented by adaptation; for example, increased red blood cell fragility may persist. Thus, adaptation or masking of some (usually acute or irritant) symptoms may occur while other physiologic alterations continue.

Individuals' abilities to adapt to ozone appear to depend on their initial sensitivity to it. More sensitive persons adapt more slowly and cannot maintain adaptation as long, usually less than seven days after exposure ceases (Horvath et al., 1981). Although adaptation to ozone may be related to what occurs in MCS, chemically sensitive patients frequently blame solvents for their symptoms (Terr, 1989; Cone et al., 1987) and adaptation to solvents has been well-documented. Vapors from various solvents are the most prevalent of indoor air contaminants (Molhave, 1982), and indoor air contaminants are of major concern to MCS patients. The volatile organic compounds associated with sick building syndrome are in large part solvent vapors.

Persons who have painted or used solvents extensively are well aware of the olfactory fatigue (nasal adaptation) that occurs and may have experienced the stimulatory and depressive (withdrawal) effects of solvents. Alcoholic beverages contain the solvent ethanol, which has related and familiar stimulatory and withdrawal effects.

Studies of xylene, one of the most prevalent solvents in indoor air, demonstrate that its effects are attenuated as exposure continues, presumably due to adaptation (Riihimaki and Savolainen, 1980). Riihimaki and Savolainen exposed healthy male volunteers to constant (100 or 200 ppm) and varying (200 or 400 ppm hourly peak) concentrations of xylene, adjusting baseline concentrations in the latter case so that a mean concentration of 100 or 200 ppm was maintained. Exposures occurred over a six-hour period (with a one-hour break at noon) for five days, followed by a two-day weekend without exposure, and one to three more days of active exposure to xylene. The investigators measured a variety of psychophysiological parameters, including reaction time, body balance, manual dexterity, and nystagmus.

Most of the adverse effects of xylene on normal subjects "tended to disappear after a few succeeding days of exposure." However, "after the weekend away from exposure, the effects were again discernible." Riihimaki and Savolainen conclude: "This phenomenon suggests that tolerance had developed over a few days with regard to psychophysiological effects by xylene."

We have mentioned several exposures that may involve adaptation. Clearly, individuals with or without multiple chemical sensitivities undergo adaptation to a wide variety of substances in their environment. However, the specific role adaptation plays in the dramatic responses patients report with MCS is not clear.

Patients may experience the effects of adaptation and de-adaptation without realizing what has occurred (Ashford and Miller, 1991). For example, a person with asthma may feel well after spending a week on a Caribbean island, breathing relatively uncontaminated air, and eating a diet devoid of usual foods. Then, exhaust emissions from the engine of a boat the individual takes to go home may bring on a severe, life-threatening asthmatic response. Back home in a metropolis, the person readapts, acclimatizes to auto emissions, combustion products and other air pollutants in the area, and experiences only chronic wheezing. Thus, following deadaptation (removal from incitants), the individual exhibits a more acute and convincing reaction upon re-exposure. This is what is reportedly observed when patients are tested in an environmental unit following deadaptation. Some of these reactions are so acute and convincing when they occur in daily life, that patients themselves may erroneously (at least in the eyes of some) surmise they must have an "allergy" to the incitant. Physicians may be skeptical and elect to challenge a patient with a supposed incitant. If, however, the patient is not deadapted or unmasked when tested, no reaction may occur, and the physician will be convinced the "allergy" was all in the patient's mind.

The deadaptation of patients may be critical to the study and the diagnosis of MCS for several reasons.

1. People are often exposed to dozens of potential incitants simultaneously, such as volatile organic compounds in a tight home or building, and literally hundreds over the course of a single day, so that health effects of these exposures may overlap, making it difficult to discern cause-and-effect relationships (Figure 1).

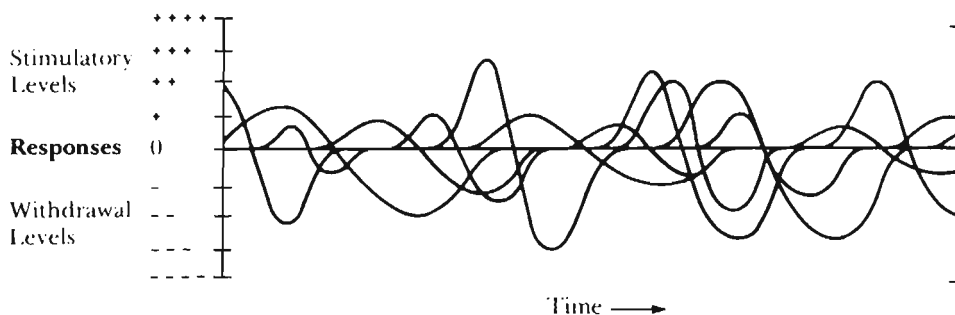


FIGURE 1. Overlapping of responses to food and chemical incitants in an individual with multiple exposures and multiple chemical sensitivities. *Source:* Ashford and Miller, 1991. Reprinted with permission of the publisher.

2. With continuous or frequent exposure to the same substance or chemically-related substances (such as xanthines in coffee, tea, chocolate, and colas), individuals adapt or develop tolerance to certain aspects of those exposures. Acute symptoms may gradually give way to chronic symptoms that may bear no apparent relationship to exposure. Exposures may never stop long enough for the patient to reach a baseline from which responses to challenges can be accurately gauged.

Graphical Representation of an Individual's Symptoms Before and After Entering an Environmental Unit

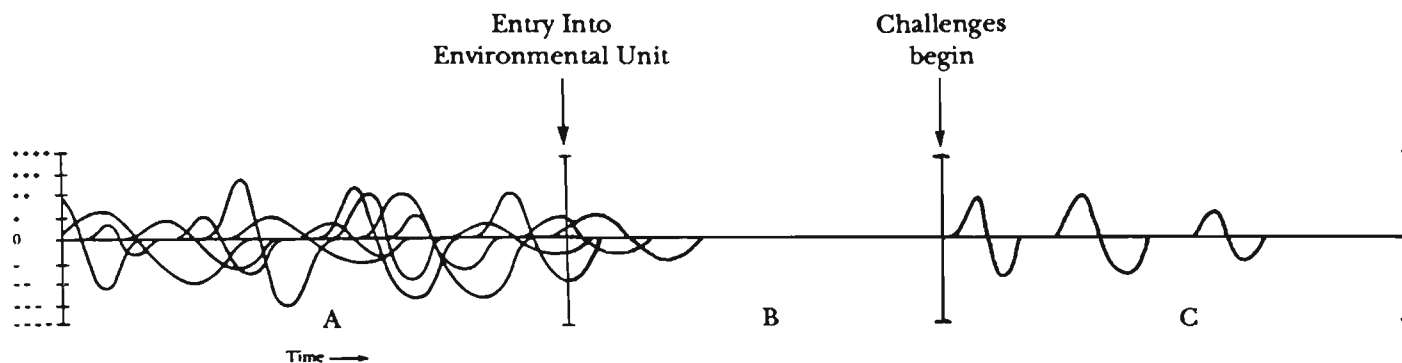


FIGURE 2. In time period A an individual is responding to multiple incitants encountered in normal daily living (chemicals and/or foods), with stimulatory and withdrawal effects that overlap in time. At any particular time, how the person feels is determined not only by ongoing exposures, but by previous exposures whose effects may still be waning. In time period B, the individual enters an environmentally controlled facility, fasting. With cessation of contributory exposures, withdrawal effects occur, for example, headache, fatigue, and myalgias. Symptoms continue for some time (typically 4-7 days) until the individual reaches "0" baseline. In some time period C, single challenges to suspected incitants are administered. Symptoms, often robust, develop soon after challenges, allowing patient and physician to begin to observe the relationship between exposures and symptoms for that individual. *Source:* Ashford and Miller, 1991. Reprinted with permission of the publisher.

Environmental units have been used to help overcome the masking effect of adaptation and the problems of overlapping exposures that result in overlapping responses to multiple agents. Such environmental units may in fact allow backing up or reversal of adaptation. Figure 2 graphically depicts the changes in symptoms that might occur in a patient who enters an environmental unit. Advantages of such an approach over conventional methods for determining toxicity may include facilitating detection of subclinical, prepathologic effects of chemicals and providing more than just a snapshot of an individual's response to substances. Removing a person from interacting, time-dependent stimuli in this way could allow the unraveling of multiple causes. Environmental units are an essential research tool. Many carefully conducted studies of chemical effects with negative or equivocal outcomes may have been flawed by failure to take adaptive mechanisms into account. The potential consequences of such an oversight are major.

Important questions that must be addressed in future studies of chemical sensitivity include:

- 1) Are subjects in a deadapted state before challenges so that extraneous exposures during and before a challenge (up to several days before) do not interfere with testing?
- 2) Are open challenges performed first to confirm that the placebo (clean air or a masking odor) is in fact a placebo and that the "active" challenge is something to which the patient has had a demonstrable response?
- 3) What is the recency and latency of the patient's exposure to the substance being tested? In other words, has enough time elapsed (about a week or so) so that the person is no longer adapted or responding to the last exposure but not too much time so that sensitivity has waned? Time elapsed since last exposure is recognized as a crucial variable in conducting challenges of patients with, for example, occupational asthma.

Carefully designed studies of deadapted patients in an environmental unit, using double-blind, placebo-controlled challenges, are an essential first step for helping resolve current professional antagonisms and placing this subject on a scientific footing.

POSSIBLE MECHANISMS FOR MCS: THE LIMBIC SYSTEM²

The most frequently cited physiologic theories to explain chemical sensitivity involve the nervous system, the immune system, or an interaction between them, because these two systems most clearly link the external environment and the internal milieu. Both can respond to exquisitely low concentrations of chemicals. The rapid responsiveness of these systems also makes them attractive candidates because symptoms of food or chemical sensitivity have been

² Modified in part from Ashford, N.A. and Miller, C.S. (1991). *Chemical Exposures: Low Levels and High Stakes*. Van Nostrand Reinhold, New York.

reported to develop within seconds of exposure. Many chemicals, such as polybrominated biphenyls (PBBs) and trichloroethylene, affect both the nervous system and the immune system. Until 1980, the idea that direct communication between the nervous and immune systems might occur was widely debated. Subsequently, the existence of a neuroimmunoendocrine axis has been increasingly realized. Several discoveries have helped to confirm the presence of two-way communication between the nervous and immune systems (Payan et al., 1986).

Kilburn (1989) proposes that the human nervous system, because it is so highly evolved, may be most susceptible to environmental agents:

"Sensitivity may be its undoing. The intuitive hypothesis is advanced that the nervous system is the most liable of the body's systems to damage from environmental toxins. Appreciation of damage may be masked because subtle dysfunction is concealed by the nervous system's remarkable redundancy and substitution of functions, or it is overlooked in clinical evaluations which are usually only qualitative."

The hypothalamus, which is in close association with the limbic system, has attracted considerable attention because it is the focal point in the brain where the immune, nervous, and endocrine systems interact (Bell, 1982). Bell notes that assuming a direct cause-and-effect relationship would be premature, but that the hypothalamus could mediate food and chemical addictions in patients with multiple chemical sensitivities. The olfactory system has known links to the hypothalamus and other parts of the limbic system, which has led Bell to speculate that "the olfactory system, hypothalamus and limbic system pathways would provide the neural circuitry by which adverse food and chemical reactions could trigger certain neural, psychologic and psychiatric abnormalities." Patients with chemical sensitivities have reported food cravings, binges, violence, or hypersexual activity following chemical exposures. A model involving the hypothalamus could help explain such behavioral changes.

Some authors have alleged that psychologic conditioning to odors is responsible for patients' reactions to chemicals. Of course, odor conditioning could be involved in selected cases. However, physiologic mechanisms involving the limbic system may also occur. A direct pathway from the oropharynx to the brain and the hypothalamic and limbic region has been demonstrated in rats (Kare, 1968; Maller et al., 1967). Substances placed in the oropharynx migrated to the brain in minutes via a pathway other than the blood stream and in higher concentrations than if administered via the gastrointestinal tract, suggesting a direct route from mouth to brain. Similarly, Shipley (1985) showed that inhaled substances that contact the nasal epithelium may cross into the brain and be distributed widely via transneuronal transport. Thus, molecules that are inhaled and contact the olfactory apparatus could conceivably influence functions in other parts of the brain.

Ryan and associates (1988) studied 17 workers who attributed changes in thought processes, particularly memory and concentration difficulties, or changes in mood, to their exposure to

solvents. Workers with "cacostmia" (a heightened sensitivity to odors resembling that reported by chemically sensitive individuals) performed most poorly on neurobehavioral tests requiring verbal learning or visual memory. The authors believed their findings supported a hypothesis that chronic solvent exposure may affect the "rhinencephalic structures" (primitive "smell" brain), the evolutionary precursor of the limbic system.

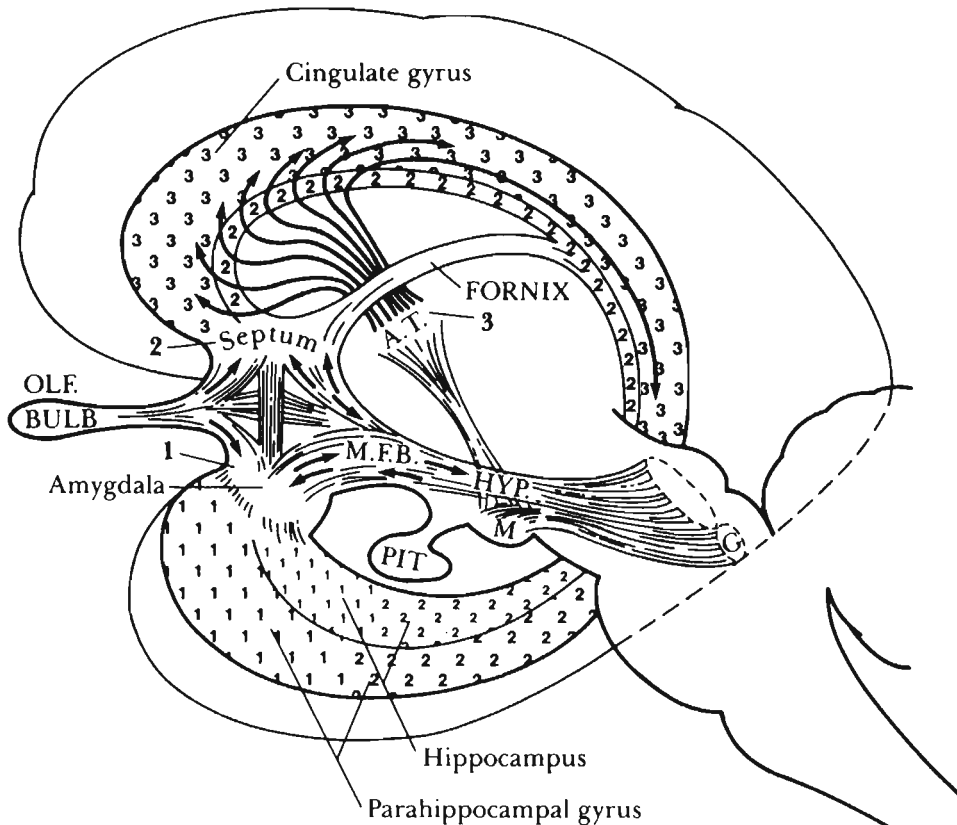


FIGURE 3. Three major subdivisions of the limbic system. The small numerals 1, 2, and 3 overlies, respectively, the amygdaloid, septal, and thalamocingulate divisions. The corresponding large numerals identify connecting nuclei in the amygdala, septum, and anterior thalamus. Abbreviations: AT, anterior thalamic nuclei; G, tegmental nuclei of Gudden; HYP, hypothalamus; M, mamillary bodies; MFB, median forebrain bundle; PIT, pituitary; OLF, olfactory. *Source:* MacLean, 1973. Reprinted with permission of the publisher.

This phylogenetically ancient part of the brain is present in all mammals. It influences the organism's interaction with its environment in many subtle ways essential for preservation of the individual, its offspring, and the species. Limbus (Latin for "margin" or "rim") refers to its rim-like appearance around the inner edge of the cerebral hemispheres. Figure 3 shows its component parts. Note the close anatomical relationship to the olfactory bulb. The olfactory nerves are the brain's most direct contact with the external environment. No protective blood-brain barrier exists here. Each olfactory nerve consists of bipolar neurons with one end in the upper part of the nose and the other in the brain (olfactory bulb). Odors can elicit electrical activity in the amygdala and hippocampal areas of the limbic system via this pathway.

(Monroe, 1986). Subsensory exposure to chemicals may 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 (Bokina et al., 1976). All parts of the limbic system are intimately interconnected. Interestingly, ablation of the olfactory bulb in laboratory animals serves as a model for depression that investigators have used to test the efficacy of various antidepressants (Jesberger and Richardson, 1988).

The amygdala, the most sensitive portion of the brain to chemical stimuli, is involved in feelings and activities related to self-preservation, such as searching for food, feeding, fighting, and self-protection (MacLean, 1986). It has been dubbed "emotion central," signifying its importance in mood states. The cingulate gyrus appears to influence maternal care and nursing, separation cries between mother and offspring, and playful behavior, including wit and humor (MacLean, 1986), qualities that many MCS patients feel have been impaired. The septum involves feeling and expression relating to procreation. Lesions in the septal area may cause hyperresponsiveness to physical stimuli (such as touching, sounds, or temperature changes), hyperemotionality, loss of motivation, excessive sugar and water intake, and fear of unfamiliar situations (Isaacson, 1982), phenomena reported by some chemically sensitive individuals.

Another limbic region, the hippocampus, appears important for laying down new memories and is thus essential for learning (Gilman and Winans, 1982). Hippocampal lesions may cause difficulty in retaining recent memories (Isaacson, 1982). The hippocampus, at the intersection of numerous neural pathways and in a critical position to affect the transfer of information from one brain region to another, acts as an information switching center. 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 (Office of Technology Assessment, 1990; Walsh and Emerich, 1988). Damage to the hippocampus itself, or to nerves leading to or from it, may adversely affect the synthesis, storage, release, or inactivation of the excitatory and inhibitory amino acids that serve as neurotransmitters in this region of the brain. Toxins may disrupt the delicate balance of these amino acids, perhaps leading to the release of a flood of excitatory neurotransmitters that damage neighboring cells, a phenomenon that has been called "excitotoxicity" (Office of Technology Assessment, 1990). Remarkably small perturbations of hippocampal function may have large and long-lasting effects on behavior and cognition (Walsh and Emerich, 1988).

The hypothalamus, which interacts closely with the limbic region, governs (1) body temperature via vasoconstriction, shivering, vasodilation, sweating, fever, and behaviors such as moving to a cooler or warmer environment or putting on or taking off clothing; (2) reproductive physiology and behavior; (3) feeding, drinking, digestive, and metabolic activities, including water balance, addictive eating, and complete refusal of food and water leading to death; (4) aggressive behavior and physical manifestations of emotion such as increased heart rate, elevated blood pressure, dry mouth, and gastrointestinal responses (Gilman and Winans, 1982).

The hypothalamus is also the locus at which sympathetic and parasympathetic nervous systems converge. Many symptoms that patients experience with food and chemical sensitivities could be related to the autonomic nervous system. For example, altered smooth muscle tone produces Raynaud's phenomenon, diarrhea, constipation, and other symptoms reported by these individuals. The hypothalamus also appears to influence anaphylaxis and other aspects of immunity (Stein et al., 1981). Conversely, antigens may affect electrical activity in the hypothalamus (Besedovsky et al., 1977).

It is important also to recognize that thoughts arising in the cerebral cortex that have strong emotional overtones may trigger hypothalamic responses and recreate the physical effects associated with intense anger, fear, and other feelings. To implement its effects, the hypothalamus not only has a direct electrical output to the nervous system but also produces its own hormones, many of which stimulate or inhibit the pituitary's production of hormones (Gilman and Winans, 1982).

Most of the neural input to the hypothalamus comes from the nearby limbic and olfactory areas (Isaacson, 1982). Lesions in the limbic region may be associated with irrational fears, feelings of strangeness or unreality, wishing to be alone, and sadness (MacLean, 1967). A feeling of being out of touch with or out of control of one's feelings and thoughts, not unlike that described by many patients with chemical sensitivity, may be perceived. Some patients report feeling "spacey" or that "the camera isn't on" unless they make an enormous effort to focus their attention.

Doane and Livingston (1986) describe potential difficulties for patients with limbic dysfunction. "Activity controlled by the limbic system may seem largely irrational and often is not perceived within one's self in ways that are easily understood or communicated in verbal language."

The dynamic involvement of the hypothalamus and limbic system in virtually every aspect of human physiology and behavior makes injury to these structures an intriguing hypothesis to explain the development of chemical sensitivity with its diverse manifestations. Rich neural connections lie between the olfactory system and the limbic and temporal regions of the brain. Surgical or epileptic patients with damage to the limbic or medial temporal portions of the brain may experience persistent alterations in odor perception (for example, an unusual smell that characteristically precedes seizure activity), as well as learning and memory difficulties (Ryan et al., 1988).

Bell (1990) hypothesizes that chemically sensitive patients may have olfactory-limbic-temporal pathways that are more easily "kindled." In other words, a small signal or insult would more readily trigger firing of nerve cells in brain regions where kindling was present. Kindling might be enhanced by genetic endowment, prior environmental exposures,

psychologic stress, hormonal variations, nutritional or other factors. Unlike surgical ablation, which destroys a brain area, kindling is a kind of stimulatory lesion (Girgis, 1986). Kindling has previously been described in the context of seizures. The amygdala, for example, which is particularly susceptible to electrical discharge following either electrical (Girgis, 1986) or chemical provocation (Bokina et al., 1976), is subject to long-lasting alteration when strong or repetitive stimuli are administered. Very potent or repeated stimuli, whether electrical or chemical, may permanently augment the tendency for neurons to fire in the presence of future stimuli, even when challenged with much lower levels than those originally involved.

Girgis (1986) reports a decrease in acetylcholinesterase (AChE), an enzyme that breaks down the neurotransmitter acetylcholine in junctions between nerve cells, that parallels the increase in supersensitivity to stimuli. The limbic system is especially rich in AChE, which is strongly bound to the nerve cell membranes and is very stable. 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" (Girgis, 1986). Interestingly, physicians who see patients with chemical sensitivities have noted that some of the most severe and debilitating exposures for these patients have involved organophosphate pesticides, which inhibit AChE (Ashford and Miller, 1991; Rosenthal and Cameron, 1991) and have reported that these patients may be especially sensitive to the anticholinergic properties of drugs (Schottenfeld, 1987).

Animals primed by high or repeated lower concentrations of various chemicals, such as formaldehyde or ozone, and subsequently re-exposed to low concentrations of the same chemicals showed an increased tendency toward paroxysmal electrical discharge in the amygdala (Bokina et al., 1976). Bokina observed that although the chemicals he used to sensitize the animals were different in terms of their structure and physical and chemical properties, their effects on the limbic system were remarkably similar, paralleling observations in MCS.

Kindling could help explain the apparent loss of adaptive capacity and spreading of sensitivities to chemically unrelated substances reported in multiple chemical sensitivity. Formerly well-tolerated, low-level exposures to, for example, tobacco smoke or perfume might trigger symptoms in individuals whose limbic areas had been kindled by a prior pesticide or solvent exposure.

One intriguing aspect of the limbic system as a possible mechanism for multiple chemical sensitivities is the system's responsiveness to both chemical and cortical stimuli. Therefore, conscious thought processes and emotional states may influence limbic activity just as chemical or physical stimuli can. The former may be under more or less conscious control of the individual, whereas the latter are almost entirely unconscious and automatic. However, conscious efforts that play into the delicate circuitry of the limbic system may be able to alter or suppress concurrent electrical activity evoked by environmental agents. Some patients with chemical sensitivities report being able to "will" their way out of a mild reaction to a food or

chemical, and attempt to control their symptoms in this manner. Most patients, however, say such efforts do not work for their most problematic incitants. In fact, the ability to exercise any conscious effort, even that of simply getting away from the exposure, reportedly may be lost during a reaction.

Monroe (1986) described a man for whom exposure to the odor of stale beer caused greatly increased electrical activity in the limbic area (amygdala and hippocampal areas). Various memories, some associated with beer, also increased electrical activity in the same region. However, simple arithmetic computations would immediately stop such activity. Therefore, conscious thought processes could alter some electrical activity in the limbic system.

Detection of chemical stimuli in the nose is not limited to the olfactory nerve but involves the trigeminal nerve and its afferens, 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 (Silver and Maruniak, 1981). This powerful reflex serves an obvious protective role. Most familiar is the trigeminal reflex response to smelling salts. Apparently trigeminal responses can occur with non-irritating stimuli. Thus far, no odor has been found that stimulates the trigeminal nerve alone or the olfactory nerve alone (Silver and Maruniak, 1981) making study of either system in isolation difficult. Potentially both play a role in chemical sensitivity.

SUMMARY

Conceivably, chemicals contacting olfactory nerve projections in the nose could either be transported into or relay electrical signals to the limbic region, leading to a vast array of symptoms. Likewise, thought processes and mood states may trigger or interrupt pre-existing limbic activity. At present, however, no evidence suggests that limbic activity triggered by environmental exposures can be entirely overcome by psychologic interventions. One important ramification of a limbic hypothesis, if true, is that no convenient biologic marker for multiple chemical sensitivity may exist at the present time.

Ten years from now, we may finally confirm the existence of multiple chemical sensitivities (by careful, blinded challenges) but still have no single mechanism to explain it; that is, after all avenues of biochemical and immunologic inquiry have been exhausted, no single cause or marker for this disorder may be apparent. The theory that adaptation plays a role in MCS is based on the observed responses of patients in a deadadapted state who have been housed in an environmental unit. Although adaptation is only an observation at this time, not a mechanism, biologic limits might regulate how much an organism can adapt. Such limits could be highly individual and vary by orders of magnitude. Certainly adaptation occurs at all levels of biologic systems, from enzyme systems to cells, tissues, organs, and even behavior

(Fregly, 1969). Theoretically, a major insult or the accumulation of lower-level injuries within these systems could lead to a kind of "overload" or "saturation" effect with respect to adaptive capacity. This might cause an individual to have environmental responses, which, instead of being flexible and fluid, would become fragile and overly responsive. Many MCS patients report that years, and in some cases decades, after the onset of their problems, they have recovered only a portion of their former energies and tolerance for their environment. Their descriptions seem to suggest the loss of an intangible capacity to adapt, parts of which may be temporary and recoverable and other parts of which may not. Perhaps our patients have been telling us the diagnosis.

*And so these men of Hindostan
Disputed loud and long,
Each in his own opinion
Exceeding stiff and strong,
Though each was partly in the right,
And each was partly wrong.*

J.G. Saxe

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