WHITE PAPER: CHEMICAL SENSITIVITY: HISTORY AND PHENOMENOLOGY

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Nearly everyone has heard something about chemical sensitivity, either from personal experience with someone who has the condition or from the media. The television series Northern Exposure recently featured a chemically sensitive attorney who lived in a geodesic dome in Alaska, and L.A. Law depicted the struggles of a Persian Gulf veteran with chemical sensitivities who lost his case against the Veterans Administration, but may appeal later in the season. Television news programs and the printed media have showcased patients living spartan existences in remote areas or in aluminum foil-lined rooms. Our views of the illness no doubt are colored by our own personal experiences of it. While some discount or make jokes about chemical sensitivity or these patients, physicians who have seen a number of them are discovering that many appear to be credible individuals with prior good work records who say they became ill following an identifiable exposure to chemicals.

HISTORICAL OVERVIEW

Chemical sensitivity was first described about 40 years ago by an allergist named Theron Randolph who practiced in Chicago. His first patient was a physician's wife and cosmetic saleswoman with rhinitis, asthma, headache, fatigue, irritability, depression, weight swings, and intermittent loss of consciousness, who reported that each time she drove from her home in southern Michigan to his office in Chicago she became ill while passing through the heavily industrialized areas of northwest Indiana and South Chicago (Randolph, 1987). There appeared to be a common thread to her complaints — she reported becoming ill when exposed to combustion products and other derivatives of gas, oil, or coal. Similar patients with the "petrochemical problem," as Randolph called it, followed. Patients were advised to avoid a wide range of everyday chemical exposures and foods to see whether they improved, and, if so, to reintroduce single substances one at a time while observing the effect of each.

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Randolph's approach toward these patients was, and continues to be, vehemently opposed by other physicians, particularly some allergists, who have been critical of the anecdotal nature of his work, his reliance upon patients' self-reporting of symptoms, and certain diagnostic practices and treatments adopted by his followers who became known as "clinical ecologists." These practices include sauna therapy, vitamin and mineral supplementation, and sublingual or intradermal administration of chemicals to diagnose and treat the condition. Position papers by the California Medical Association (1986), the American College of Physicians (1989), the American Academy of Allergy and Immunology (1986), and other physician groups have criticized the ecologists for a lack of critical thinking and use of unproven practices. Clinical ecology has been labelled as "junk science," a "medical subculture," and its patients as "true believers" (Brodsky, 1987; Staudenmayer and Selner, 1987; Huber, 1991). In contrast, others regard chemical sensitivity as a potentially real and growing problem and, to some degree, view such attacks on the clinical ecologists as "killing the messenger."

An acrimonious debate between allergists and clinical ecologists concerning this condition and how to treat it has been ongoing for nearly a decade in professional meetings, medical journals, and courtrooms. Other voices recently have joined in — e.g., those of occupational medical physicians and environmental health researchers. Over the past five years, more and more patients reporting chemical sensitivity have sought the help of academically-based occupational medicine physicians.

Two recent books and two reports written by academicians for the states of Maryland and New Jersey on chemical sensitivity have brought focus to the subject (Cullen, 1987; Ashford and Miller, 1989, 1991; Bascom, 1989). The New Jersey Report on chemical sensitivity suggested that legitimate professional concerns over unorthodox diagnostic and treatment approaches employed by the clinical ecologists be separated carefully from the question "Does chemical sensitivity exist as a clinical entity?" In the spring of 1991, in response to growing public and professional interest in chemical sensitivity, the National Research Council (NRC) convened a workshop to develop research recommendations for multiple chemical sensitivity or "MCS," as it has come to be called. Clinicians, toxicologists, immunologists, epidemiologists, psychiatrists, psychologists, and others with relevant skills or interests were invited to attend. The Environmental Protection Agency (EPA) and the National Institute of Environmental Health Sciences (NIEHS) shared sponsorship and the Agency for Toxic Substances and Disease Registry (ATSDR) provided ancillary support for the meeting. Participants offered diverse perspectives and achieved consensus as to future research directions, despite general concern that "definition of the phenomenon was elusive and its existence as a distinct clinical entity had not been confirmed" (National Research Council, 1992).

In the fall of 1991, ATSDR sponsored the second national meeting devoted exclusively to MCS in conjunction with the Association of Occupational and Environmental Clinics (AOEC), inviting occupational medicine physicians from across the country. Participants agreed that there were many unanswered questions about the illness and that further research

on MCS was needed. In the past three years, a handful of academic researchers have applied for federal funding for MCS-related projects and a few, small pilot studies have been funded.

One problem that mitigates funding agencies' willingness to support studies on MCS is the fact that there is no reliable estimate of the number of patients affected by it. In part, this is due to lack of an agreed-upon case definition. What is known about the size of the problem is that approximately twenty MCS patient newsletters are published, including some with national circulations and several thousand subscribers apiece. Recently, the Social Security Administration and Housing and Urban Development (HUD) have recognized MCS as a disability, despite the fact that there is no generally accepted case definition, no identified mechanism for the disorder, and no laboratory marker to confirm its presence. The Americans with Disabilities Act (ADA) also affords some protections, on a case by case basis, to those disabled by MCS. Some fear that the illness is rapidly becoming politically defined before there is adequate science to support its existence.

FEDERAL AGENCY INTEREST

With growing public concern and litigation over MCS, several federal agencies now find themselves facing important policy questions related to the condition. One of these agencies is the Environmental Protection Agency (EPA). The EPA's mission includes preventing adverse human health effects from pesticides and indoor air pollution. Many MCS patients point to pesticides or sick buildings as the original causes of their illness. Ironically, several years ago the EPA itself installed 27,000 square yards of new carpeting, painted and remodeled space in its Waterside Mall headquarters in Washington, D.C., and had the unwelcome opportunity to study MCS firsthand (Ashford and Miller, 1991). Out of 200 or so agency employees who developed symptoms associated with sick building syndrome, several dozen reported developing MCS. These employees complained of being unable to tolerate tobacco smoke, perfume, engine exhaust, and other low-level exposures that they say had not been a problem for them before the remodeling took place. Some left the agency claiming they could no longer work. Some went to other jobs or now work at home. Some moved into specially-furnished offices the EPA provided which had no carpeting, disinfectants, perfume, etc., and where occupants could open windows. Litigation currently is in process. Nationwide, indoor air pollution is estimated to cost tens of billions of dollars annually (Environmental Protection Agency, 1989). MCS cases are part of this costly burden, exacting an enormous financial toll on patients, building owners, and product manufacturers. In addition to helping sponsor the NAS meeting on MCS, the EPA recently initiated its own in-house study to characterize the condition.

About a year ago, the U.S. Congress asked the Agency for Toxic Substances and Disease Registry (ATSDR) to direct $250,000 from its budget toward chemical sensitivity and low-level environmental exposure workshops. In the spring of 1993, ATSDR convened a panel of physicians, scientists, and MCS patients who recommended that a conference be held to explore the extent to which the central nervous system might be involved in the disorder.

Superfund monies fund ATSDR to investigate and provide information regarding health effects related to toxic wastes. Many citizens who live near Superfund hazardous waste sites report being ill, yet exposures frequently are "low-level," that is, well below recognized safety limits. Consequently, ATSDR is interested in a wide range of possible health effects from low-level chemical exposures, including MCS. Thus far, twelve hundred toxic waste dump sites have been placed on a national priority list for remediation out of an estimated 400,000 sites throughout the United States. Nevertheless, there is a paucity of data concerning health effects associated with most of the exposures involved. Billions of dollars have been spent for clean-up of Superfund hazardous waste sites over the past decade, and results of research on MCS could affect future policy and expenditures in this area in important ways.

In the past year, the Department of Veterans Affairs (DVA) and Department of Defense also have been drawn into the MCS debate. Many Persian Gulf veterans returned from the War complaining of multi-system health problems, such as fatigue, depression, irritability, memory and concentration difficulties, muscle aches, shortness of breath, diarrhea, and a host of other problems which they attribute to exposures in the Gulf. Exposures included combustion products from oil well fires, paints, fuels, pesticides, solvents, and others. Some congressmen and veterans have raised the specter of possible chemical or biological war agent use. A number of veterans have expressed dissatisfaction with the DVA's inability to link their illnesses with their wartime exposures and have sought help from clinical ecologists in private practice who in turn have diagnosed them as having MCS. Some veterans who have seen clinical ecologists subsequently have tried to obtain medical benefits and compensation from the DVA for war-related injuries only to be told that MCS is not a recognized medical condition. Angry, frustrated and sick, more and more veterans have turned to their legislators for assistance. In early 1994, the DVA issued a request for proposals to establish Environmental Hazards Research Centers in up to three VA hospitals. Researchers in these centers would focus on the role of environmental exposures in the Gulf veterans' health problems, including chemical sensitivity.

Thus, a growing number of federal agencies involved in occupational and environmental health issues, including the EPA, ATSDR, DOD, and the DVA, but also NIEHS, OSHA (Occupational Safety and Health Administration), and NIOSH (National Institute for Occupational Safety and Health), have encountered MCS, and several of these agencies have become interested in advancing scientific knowledge concerning this condition. In the past five years, the controversies surrounding MCS have exploded far beyond the narrow confines of a professional dispute between allergists and ecologists into a national debate with far-reaching policy and regulatory implications.

OPPOSING VIEWS OF THE ILLNESS

A wide variety of names have been applied to MCS and to those affected by it. Many of the names themselves seem to invite controversy.

Terms for the condition:

- Multiple Chemical Sensitivity (MCS)
- Chemical Sensitivity
- Environmental Illness (EI)
- Cerebral Allergy
- Twentieth Century Disease
- Chemically-induced Immune Dysregulation
- Total Allergy Syndrome
- Ecologic Illness
- Chemical Hypersensitivity Syndrome
- Environmental Maladaptation Syndrome
- Universal Allergy
- Chemical AIDS

Terms patients use to describe themselves:

- universal reactors
- canaries
- chemies

Those who feel MCS is the consequence of chemical exposures point to the exponential rise in the use of synthetic organic chemicals and pesticides in homes and workplaces since World War II; to the construction of "tight," energy-efficient housing, offices, and commercial buildings since the oil embargo of the 1970s, with consequent reduction in fresh air indoors and higher volatile organic chemical (VOC) levels inside buildings; and to the fact that the average American now spends 90% or more of the day indoors. Indeed, EPA studies have demonstrated that indoor concentrations of certain VOCs may be orders of magnitude above outdoor levels (Wallace, 1985). Besides outgassing from interior finishes and furnishings, VOCs and other pollutants might emanate from toxic waste sites, percolate up from the soil via foundation cracks and crevices (e.g., unsealed pipe runs) into structures, and accumulate indoors, analogous to radon. MCS proponents point out that Americans living today are the first of their species to live indoors with relatively high levels of a peculiar mix of VOCs.

MCS patients often attribute onset of their illness to a specific exposure, for example, a chemical spill, repeated exposure to a solvent, application of a pesticide, a sick building or combustion products from a fire. Subsequently, patients generally report that they experience their greatest difficulties indoors where perfume, air fresheners, cleaners, etc., are used and interior finishes or furnishings such as carpet or particle-board "outgas," releasing VOCs.

MCS patients express frustration with many physicians, whom they perceive as not believing them and not understanding that their symptoms are caused by chemical exposures. A number of patients are teachers, lawyers, health care providers, and other professionals who appear to be credible historians and who say they experience reproducible symptoms with specific exposures, e.g., to tobacco smoke, a certain perfume, etc. They express anger toward

physicians who prescribe antidepressants or who refer them to psychiatrists or psychologists. From the patients' perspectives, they have lost their health, their livelihoods, and many of their pleasures in life, while skeptical physicians treat them as psychological patients or malingerers, and cast doubt among the patients' families, friends, and employers concerning the reality of their condition.

Clinicians who question the existence of an organic basis for MCS point to the ongoing medical debate and lack of a generally accepted case definition, although several definitions have been proposed (Table 1). Some skeptics feel that well-established diagnoses, such as somatoform disorder, depression, asthma, migraine, post–traumatic stress disorder, and other conditions, account for symptoms in the majority of cases. Some practitioners believe that MCS patients hold an inappropriate belief that chemicals are causing illness. Some feel patients can be deprogrammed from their beliefs (Selner, 1988). Skeptics point to other problems with the illness, including the absence of a clinical or laboratory marker and the lack of an identified mechanism for the condition. MCS patients, who are notorious for the panoply of distressing symptoms they report, may not always realize how physicians perceive their litany of complaints — in medical school, young doctors-to-be often are taught that the more symptoms a patient reports, the less likely there is anything to them, i.e., the diagnosis is probably a psychological one.

Clinicians who view MCS as a possible new diagnosis point out that before multiple sclerosis was known as "multiple sclerosis" and before lupus was known as "lupus," there was an interim phase during which clinicians simply observed some patients with novel presentations who seemed to share certain features in common. A number of physicians and scientists believe that MCS currently may be in such an early observational stage.

CLINICAL OBSERVATIONS AND PHENOMENOLOGY

Of necessity, clinical observations concerning an illness generally precede case definitions, the discovery of markers, and elucidation of mechanisms. It has been observed that many cases of MCS appear to involve a two-step process (Figure 1) (Ashford and Miller, 1991):

1. *Sensitization*, also referred to as "priming" or "induction." In many MCS patients, symptoms appear to develop following a major exposure to any of a wide range of environmental chemicals. The "sensitizing event" may be either an acute high-level exposure, such as a chemical spill, or it may be a chronic (repeated or continuous) exposure, occurring at much lower levels, for example, a sick building. The nature of the events MCS patients say led to their illness is extraordinarily diverse and includes exposures to pesticides, solvents, combustion products, indoor air pollutants, drugs, anesthetics, and, in a few instances, extreme stress without any obvious chemical exposure.

TABLE 1. Proposed Case Definitions for Multiple Chemical Sensitivity

Ashford and Miller (1989):

The patient with multiple chemical sensitivities can be discovered by removal from the suspected offending agents and by rechallenge, after an appropriate interval, under strictly controlled environmental conditions. Causality is inferred by the clearing of symptoms with removal from the offending environment and recurrence of symptoms with specific challenge.

Association of Environmental and Occupational Clinics 1992 Workshop on Multiple Chemical Sensitivity, Working Group on Characterizing Patients:

- A change in health status identified by the patient
- Symptoms triggered regularly by multiple stimuli
- Symptoms experienced for at least six months
- A defined set of symptoms reported by patients
- Symptoms that occur in three or more organ systems
- Exclusion of patients with other medical conditions (psychiatric conditions are not considered exclusionary)

Clinical Ecologists (definition appearing in each issue of the journal *Clinical Ecology*):

Ecologic illness is a chronic multi-system disorder, usually polysymptomatic, caused by adverse reactions to environmental incitants, modified by individual susceptibility and specific adaptation. The incitants are present in air, water, food, drugs, and our habitat.

Cullen (1987):

Multiple chemical sensitivities (MCS) is an acquired disorder characterized by recurrent symptoms, referable to multiple organ systems, occurring in response to demonstrable exposure to many chemically unrelated compounds at doses far below those established in the general population to cause harmful effects. No single widely accepted test of physiologic function can be shown to correlate with symptoms.

Nethercott et al. (1993):

1. The symptoms are reproducible with exposure.
2. The condition is chronic.
3. Low-level exposure results in manifestations of syndrome.
4. Symptoms improve or resolve when incitants are removed.
5. Responses occur to multiple, chemically unrelated substances.

National Research Council (1992), Workshop on Multiple Chemical Sensitivities, Working Group on Research Protocol for Clinical Evaluation:

1. Sensitivity to chemicals. By sensitivity we mean symptoms or signs related to chemical exposures at levels tolerated by the population at large that is distinct from such well recognized hypersensitivity phenomena as IgE-mediated immediate hypersensitivity reactions, contact dermatitis, and hypersensitivity pneumonitis.
2. Sensitivity may be expressed as symptoms and signs in one or more organ systems.
3. Symptoms and signs wax and wane with exposures.

It is not necessary to identify a chemical exposure associated with the onset of the condition. Preexistent or concurrent conditions, e.g., asthma, arthritis, somatization disorder, or depression, should not exclude patients from consideration.

2. *Triggering*. Following sensitization, patients report that extremely low levels of common chemicals tolerated by the majority of the population, for example, tobacco smoke, perfume, and traffic exhaust, trigger severe symptoms. Commonly, they report that, in addition to the chemicals involved in the original exposure event, over time more and more *chemically unrelated* substances trigger symptoms. The latter observation is referred to by patients as the "spreading phenomenon."

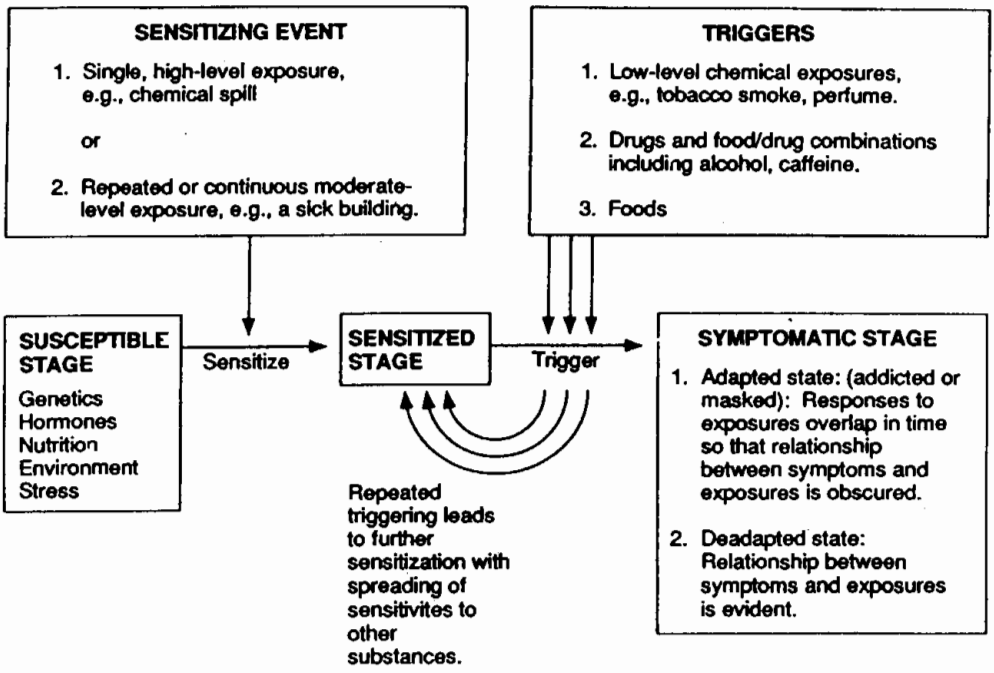

FIGURE 1. Phenomenology of Multiple Chemical Sensitivity.

This two-step process, sensitization and triggering, is reminiscent of allergic sensitization. Indeed, these patients often describe themselves as being allergic. Notably, when von Pirquet first coined the word "allergy" in 1906, he defined it as "altered reactivity" of whatever origin. However, in the 1920s, following the discovery of antibodies, allergy was redefined in immunological terms over the protests of some allergists who cautioned that certain nonimmunologic forms of hypersensitivity might be excluded. The discovery of IgE in 1967 further solidified the immunologic view of allergy.[1]

[1]Early in the development of their specialty, allergists had been accused by their colleagues of practicing witchcraft or "voodoo" medicine when they treated their patients by injecting them with tiny amounts of the same substances to which they reacted. With the discovery of IgE, allergists at last had a scientific basis for their practices.

MCS differs from classical allergies in at least one important respect: IgE formation is exquisitely specific for particular substances, e.g., ragweed or bee venom. In contrast, MCS patients report that their sensitivities spread to chemically unrelated substances. This discrepancy further enhances many allergists' doubts concerning MCS.

The limited data available at this time suggest that any mechanism or model that would purport to explain MCS would need to address the following clinical observations associated with this illness (Ashford and Miller, 1991):

1. Symptoms involving virtually any system in the body or several systems simultaneously, but most frequently the central nervous system (fatigue, mood changes, memory and concentration difficulties).
2. Different symptoms and severity in different individuals, even among those experiencing the same exposure.
3. *Induction* or *sensitization* by a wide range of environmental agents, including pesticides, solvents, and combustion products.
4. Subsequent *triggering* by lower levels of exposure than those involved in initial induction of the illness.
5. *Spreading* of sensitivity to other, often chemically dissimilar substances. Each substance may trigger a different but reproducible constellation of symptoms.
6. Concomitant food, alcohol, and medication intolerances, estimated to occur in a sizeable percentage of MCS patients.

Multiple chemical sensitivity has been reported among several distinct demographic groups (Table 2). To these groups might be added a fifth group — Persian Gulf veterans. When clinicians see patients one at a time (as in group 4 of Table 2), they are unlikely to attribute an individual patient's symptoms to an environmental exposure, even if the patient happens to mention the exposure (unless of course the hazard is one already well known to the physician, e.g., lead or benzene). It is especially easy to overlook environmental causes if symptoms are subjective and nonspecific, such as headache, fatigue, depression, or difficulty concentrating. Many of the first cases of MCS described involved individual, upper-middle class women. Such cases often were viewed as depression or "hysterical housewife syndrome" and referred accordingly. Notably, the first cases of sick building syndrome occurring in offices and schools were attributed to "mass psychogenic illness," rather than poor indoor air quality, before sick buildings were recognized. Physicians who happen to see a series of cases, all of whom share an identifiable exposure, are more likely to view the illness as "real" and investigate its origins. Thus, the *temporal cohesiveness* of symptoms occurring in a group of individuals sharing a recognizable exposure event, for example, several family members, co-workers, or community residents exposed to the same chemicals, helps physicians recognize the possibility of an environmentally caused illness in those circumstances. The outbreak of MCS among technical staff at the EPA headquarters who had been present during remodeling and carpet installation facilitated recognition of a possible environmentally related illness in that circumstance.

TABLE 2. Chemically Sensitive Groups (Ashford and Miller, 1991)

Group	Nature of Exposure	Demographics
Industrial workers	Acute and chronic exposure to industrial chemicals	Primarily males; blue collar; 20 to 65 years old
Sick 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, groundwater and 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; 50% 30 to 50 years old (Johnson and Rea, 1989); white, middle to upper middle class and professionals

Notably, the four groups represented in Table 2 vary greatly in terms of their age, sex, social group, and the kinds of medical specialists they consult. Nevertheless, all report onset of MCS-like symptoms following an identifiable exposure event. The *demographic diversity* of the groups reporting MCS (Gulf veterans, school children, office workers, industrial workers, etc.) also suggests the possibility that a real problem may be occurring. The complaints voiced by each of these groups appear unusual:

1. Odor intolerances. Patients frequently avoid tobacco smoke, gasoline, hairspray, cleaning agents, and many other substances because they say they feel ill around them;
2. Adverse reactions to medications or medical or dental materials, for example, anesthetics, radiographic contrast dye, antibiotics, decongestants, eye drops, suppositories;
3. Alcohol and/or caffeine intolerance; and
4. Food intolerances.

MCS patients report symptoms following inhalation, ingestion, mucosal contact, or injection of an enormous variety of substances. Sometimes they describe reacting to chemicals at concentrations below the olfactory threshold. Some have no sense of smell (anosmia), yet report reactions to chemicals. Symptoms are said to begin as soon as a few seconds after the exposure. Some note that breathing through their mouths instead of their noses slows the onset of symptoms, and they report using this mouth-breathing technique to their advantage, for example, when entering an elevator where passengers are wearing perfume. Some patients report not only being overly sensitive to chemicals, but also to physical stimuli, such as bright light, noise, and being touched, not unlike some post–traumatic stress disorder (PTSD) patients. They may complain of extreme discomfort just from someone bumping their bed or from hearing conversational-level noises. Some describe feeling as though the amplitude or

gain in their nervous systems were turned up too high. Except for military and industrial populations that are primarily male, most samples of MCS patients have been predominantly female (in the majority of studies, approximately three-quarters of the patients have been women).

MCS patients often, but not always, have a life-long history of medical problems. Premorbidly, one group of MCS patients reported an average of 6.2 unexplained physical symptoms *prior to* their workplace exposure versus 2.9 for controls (Simon et al., 1990). Likewise, 54% of the same MCS patient group reported anxiety or depression prior to their workplace exposure versus only 4% of controls. In contrast, Fiedler and colleagues did not find that premorbid psychiatric conditions accounted for MCS in a group of eleven patients they studied (Fiedler et al., 1992). MCS proponents argue that even if some MCS patients were depressed prior to florid onset of the illness, the question still remains whether MCS is caused by depression, whether depressed people are more susceptible to MCS, or whether the prior depression was in fact the result of earlier, undiagnosed chemical or food sensitivities.

PARALLELS WITH ADDICTION

Patients' descriptions of MCS share striking parallels with alcohol and drug addiction (Randolph, 1980; Ashford and Miller, 1991). An interesting feature of MCS is the carbohydrate or other food cravings described by many patients. Some refer to themselves as "chocoholics" or report addiction to certain foods, such as baked goods, popcorn, sweets, colas, etc. Some report a past history of having sipped coffee, tea, cola or other caffeinated beverages throughout the day, carrying one of these with them wherever they went. Following a chemical exposure, for example, after driving in heavy traffic, some MCS patients report experiencing intense food cravings. MCS reportedly may interact with other appetitive behaviors: Most patients describe a loss of interest in sex; however, a few report hypersexuality especially following chemical exposures. Some MCS patients report extreme thirst in conjunction with their chemical or food reactions.

Randolph was impressed by his patients' descriptions of food cravings and compulsive eating behaviors. In addition, he observed that symptoms following chemical exposures or foods seemed to begin with "stimulatory" symptoms and terminate in "withdrawal symptoms" (Figure 2). He viewed food and chemical addiction as the base of a pyramid of addiction, with alcohol and street drugs being at the apex (Figure 3).

Notably, from our own observations and those of other clinicians familiar with this problem, MCS patients tend to shun alcohol, xanthines (including tea, cola, coffee, and chocolate), and drugs in general because their responses to these, they say, are so unpleasant. The nature of the symptoms they report seems consistent with what one might expect from a normal person who ingested large quantities of such substances. For example, MCS patients may report excessive irritability, agitation, and headaches following one cup of coffee or a chocolate bar.

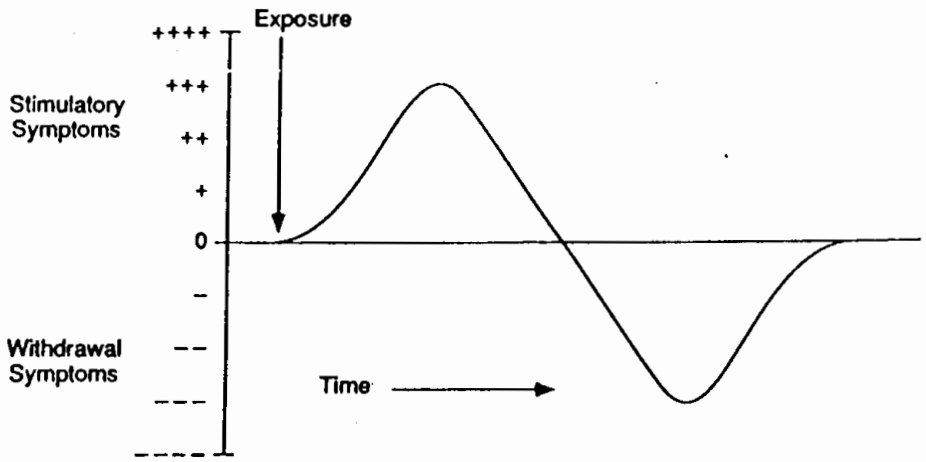

FIGURE 2. Graphical representation of symptom progression in a sensitive individual following exposure to a single substance (from O'Banion, Ecological and Nutritional Treatment of Health Disorders, 1981; courtesy of Charles C. Thomas, Publisher, Springfield, Illinois). The sine wave is a graphical representation of symptoms experienced by a sensitive individual following exposure to a *single* chemical, food, or drug. Initial symptoms, associated with the *onset* of exposure have been described as *stimulatory* in nature, for example, feeling "hyper," jittery, talkative, overly enthusiastic, anxious, or panicky. Symptoms associated with the *offset* of exposure have been described as *withdrawal* symptoms, that is, lethargy, sleepiness, depressed feelings, headache, concentration difficulties, etc. A normal individual who is not sensitive to the substance would experience no symptoms and the sine wave would be flat, with zero amplitude.

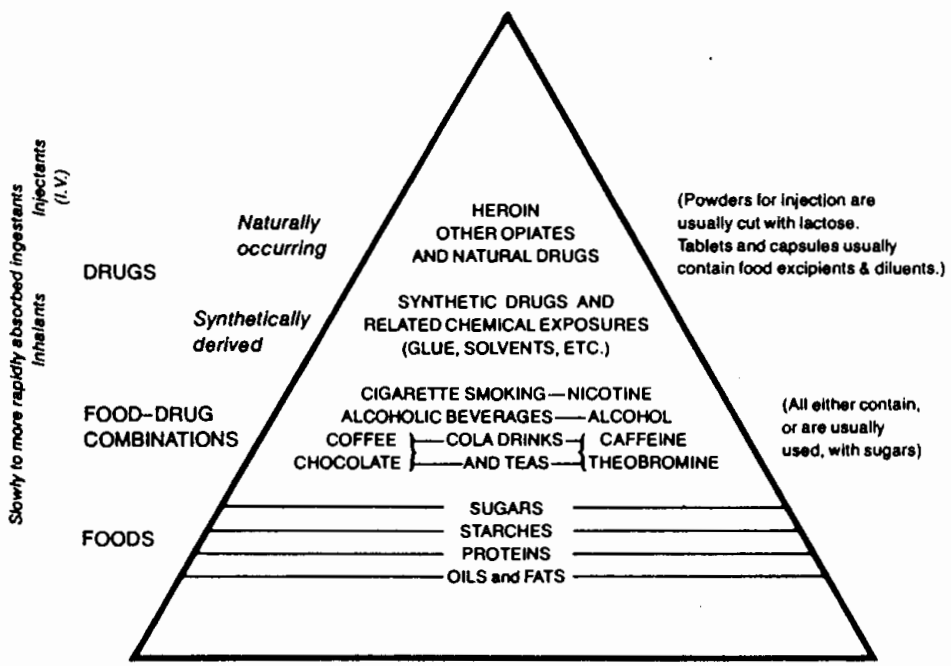

FIGURE 3. Addiction pyramid, after Randolph (1980).

Yet before they eliminated caffeine from their diets, MCS patients often say they consumed it frequently or addictively (e.g., half a pound of chocolate or 20 cups of coffee a day) and felt *chronically* ill. In this respect, MCS patients appear analogous to certain reformed smokers or alcoholics who after quitting tobacco or alcohol become exquisitely sensitive to even minute amounts of tobacco smoke or alcohol. Many MCS patients claim that they formerly were addicted to foods or chemicals, but that in the beginning the addiction was unwitting and unrecognized by them (for example, an addiction to corn or to pollutants in a sick building). Initially, when they first attempted to avoid problem chemicals and foods, MCS patients say they experienced a kind of "detox" (also called "unmasking" or "de-adaptation") accompanied by several days of intense "withdrawal" symptoms. Indeed, "detox" and "withdrawal" are terms MCS patients use to describe this experience. One patient characterized MCS as being "like drug abuse without any of the fun." The medical teaching, "Listen to the patient — he is telling you the diagnosis," would suggest that MCS patients' choice of drug addiction terminology is a clue that invites further scrutiny.

Following avoidance or "withdrawal," patients often report pronounced symptoms when they are *reexposed* to substances they appeared to tolerate before. To decipher which exposures affected which patients, Randolph developed the concept of an environmental control unit, a hospital ward that excludes disinfectants, deodorizers, strong cleaners, pesticides, perfumes, etc., and in which patients fast for several days. If patients improved in the controlled environment (and many say they did), they were then reexposed to single chemicals and foods, one at a time, to see which, if any, provoked symptoms. Tolerated foods remained in the diet, but were not to be eaten more than once every four days to prevent addiction to these from also developing. According to Randolph, "problem" foods tended to be those that were eaten frequently or addictively, such as corn, wheat, milk, or eggs. For example, he reported that some patients would drink sodas and eat candy containing corn sugar on a frequent basis and become addicted to corn without realizing it. MCS patients (once they are diagnosed as such) frequently shun alcohol, tobacco, and caffeine, and often say they are prone to addiction to foods, sugar, etc. Alcoholic beverages, such as beer or red wine, frequently are the first ingestants patients identify as causing problems. Many MCS patients say they become "hooked on" substances far less addicting than alcohol, nicotine, or caffeine and considered to have little, if any, stimulatory effect. On the other hand, certain foods contain or are metabolized to neuroactive peptides which could play a role in this process (Bell et al., 1992). In effect, MCS patients appear to be "hyper-holic," not to be confused with "hypergolic" — the property that certain rocket propellants have to ignite spontaneously upon contact between the components. The similarity between the terms, however, may not be entirely inapt.

SYMPTOMATOLOGY

Patients with this illness report multi-system health complaints. Their most frequent complaint is fatigue, which is one of the most frequent presenting symptoms of Americans who see primary care physicians (Cathebras et al., 1992). Other disabling symptoms reported by MCS patients include changes in their mood and cognitive abilities. MCS patients with

professional careers are likely to view their cognitive difficulties as the most disabling feature of their illness. Miller and Mitzel (1994) surveyed 75 MCS patients who reported onset of their illness following remodeling in a building and 37 who reported onset following exposure to a cholinesterase-inhibiting pesticide. The most frequently reported symptoms in each group were quite similar; the majority involved the central nervous system (Table 3). The most common gastrointestinal complaint was "problems digesting food," and the most common respiratory complaint was "shortness of breath or being unable to get enough air."

TABLE 3. Top 20 Symptoms (of 119 Symptoms) Reported by MCS Patients Attributing Their Illness to Pesticides (N = 37) Versus Remodeling (N = 75) (Miller and Mitzel, 1994)

	Ranking		Mean symptom severity**	
Symptom	Pesticide	Remodel	Pesticide	Remodel
*Tired or lethargic	1	1	2.49	2.44
*Fatigue > 6 months	2	3	2.43	2.10
*Memory difficulties	3	4	2.32	2.09
*Difficulty concentrating	4	2	2.32	2.17
*Dizziness, lightheadedness	5	6	2.19	1.85
*Depressed feelings	6	8	2.19	1.83
*Spacey	7	12	2.19	1.74
*Groggy	8	5	2.14	1.96
*Loss of motivation	9	7	2.11	1.84
*Tense, nervous	10	15	2.11	1.64
*Short of breath	11	18	2.11	1.61
*Irritable	12	10	2.03	1.79
Problem focusing eyes	13	43	2.03	1.27
Chest pain	14	52	2.00	1.19
*Muscle aches	15	11	2.00	1.79
Problems digesting food	16	33	1.97	1.35
*Joint pain	17	9	1.95	1.83
Tingling fingers/toes	18	59	1.95	1.12
*Headache	19	14	1.92	1.67
*Head fullness or pressure	20	19	1.92	1.60
Difficulty making decisions	21	13	1.89	1.69
Eye irritation	22	16	1.89	1.64
Slowed responses	34	17	1.72	1.63
Nausea	36	20	1.65	1.56

* = Among top 20 symptoms in both pesticide and remodeling patients.
** = Symptoms scored on 0 to 3 scale: 0 = not a problem; 1 = mild; 2 = moderate; 3 = severe.

Many patients report that exposure to a particular chemical or mixture of chemicals produces a characteristic constellation of symptoms. For example, they may say they feel spacey and have an upset stomach with diesel exhaust; become irritable when walking down the detergent aisle of a grocery store; or experience confusion around a particular perfume. Some say these symptoms are so specific that they can identify the exposure source in the absence

of any detectable odor. Individuals who shared the same initial exposure event (e.g., the EPA workers who became ill) often report markedly different symptoms. For example, one individual may report more problems with concentration, another with breathing, and still a third with digestion. This reported variability in presentation coupled with the lack of a case definition, has thwarted attempts to conduct epidemiological investigations of MCS. Following onset of their illness, many MCS patients report that their sensitivities rapidly spread to more and more chemicals, foods and drugs. If they are able to reduce their overall exposure to chemicals, some patients say they gradually regain some tolerance over a period of months and years, but that this is quickly lost if they are not continuously vigilant about minimizing their exposures.

A poorly understood, but potentially crucial, variable that may affect symptom expression and intensity is adaptation, or the development of tolerance. With repeated exposures or continuous exposure, humans adapt to many substances; acute symptoms tend to become chronic in nature and may no longer appear related to particular exposures. Adaptation has been described for substances as diverse as solvents (Riihimaki and Savolainen, 1980); ozone (Hackney et al., 1977a,b); nitroglycerin (Daum, 1983); tobacco smoke; caffeine; and many drugs (tachyphylaxis). MCS patients refer to adaptation as "masking." Many report that their illness began with "flu-like" symptoms, similar to Chronic Fatigue Syndrome. Indeed, a large number of MCS patients carry this diagnosis as well. Patients often report they were unaware of having any sensitivities to chemicals or foods in this early, flu-like stage of their illness. It was not until they avoided exposures (unintentionally, or intentionally upon someone's recommendation) that they noticed their symptoms improved. Then when they reexposed themselves (unintentionally or intentionally) to a particular environment or chemical and their symptoms recurred, they began to suspect environmental causes. This process of avoidance, whether intentional or not, has been termed "unmasking" or "deadaptation." MCS patients who travel to a large city often report that they "remask" or "adapt" and feel like they have the flu again. As long as they are "masked," they say they do not experience acute, robust symptoms with exposure to perfume or diesel exhaust — they just feel bad all of the time. Figure 4 illustrates this concept.

SUMMARY OF RESEARCH AND RESEARCH RECOMMENDATIONS

Pivotal medical, compensation, litigation, regulatory and policy questions rest upon a full understanding of MCS. Notwithstanding, remarkably little funding has been directed toward researching this illness, for a variety of reasons. Because of limited funding, the few studies that have been done have had "shoestring" budgets. Consequently, data on MCS are meager. Scientists involved in other rapidly expanding fields may find this paucity of research on an apparently vital topic surprising. Economic stakes are high. Insurers, agencies such as the DVA and DOD that provide medical care and compensation, the chemical industry, manufacturers of consumer products including carpets, building materials, fragrances and other goods could be affected greatly by the outcome of research on MCS. Some progress has occurred, however. In the past two years, two national meetings, both of which ATSDR

helped sponsor, have brought together professionals with divergent views on this subject who have made recommendations for research (Table 4).

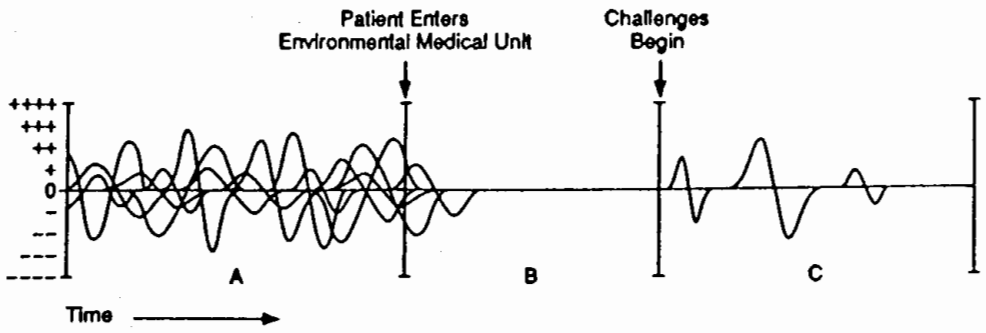

FIGURE 4. Hypothetical graphical representation of an individual's symptoms before and after entering an environmental unit (Ashford and Miller, 1991; © Van Nostrand Reinhold, 1991). In Time Period A, prior to entering an environmental medical unit (EMU), a chemically sensitive individual is responding to multiple exposures (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 also by previous exposures whose effects still may be waning. The effect of any single exposure is not discernible. Some MCS patients refer to this as being "masked." In Time Period B, the individual enters an environmental medical unit. With cessation of contributory exposures, withdrawal effects occur, for example, headache, fatigue, and muscle aches. Symptoms continue for some time (typically 4–7 days) until the individual reaches "0" (baseline). Some MCS patients refer to themselves as being "unmasked" when they are in this state, i.e., when they are avoiding all of their problem exposures. In Time Period C, single challenges to suspected chemicals or foods are administered. Symptoms, if they occur, develop soon after challenges, allowing patient and physician to observe the relationship between exposures and symptoms for that individual.

TABLE 4. Summary of Research Recommendations from Federally Sponsored Meetings on Multiple Chemical Sensitivity (MCS)

I. National Research Council meeting on Multiple Chemical Sensitivities, March, 1991 (NRC, 1992).

- A. Sponsors: EPA, ATSDR, NIEHS
- B. Participants: Invited clinicians, immunologists, toxicologists, epidemiologists, psychiatrists, psychologists, and others involved in research or clinical activity relevant to MCS
- C. Recommendations (3 groups):

1. Clinical Evaluation Group: Proposed a case definition for research (see Table 1 Proposed Case Definitions). Also suggested:
   a. Development of a uniform patient database
   b. Hypothesis-driven specialized evaluations
   c. Development of an environmental control unit for study of adaptation/deadaptation hypothesis, control of exposures, and challenging subjects
   d. Prospective studies of exposure events
2. Exposures and Mechanisms Group

a. Double-blind controlled exposure challenges, examining the possible role of "adaptation" and "deadaptation"
b. Evaluation of MCS patients in their usual environment, as symptoms and exposures vary over time
c. Development of animal models that mimic the human syndrome
d. Evaluation of biopsy or necropsy tissue for pathologic changes
e. Development of database of chemicals, foods, drugs, and associated symptoms and signs

3. Epidemiology Working Group
   a. Improvement of case definition
   b. Multi-center clinical case-comparison studies using agreed-upon set of criteria and tests
   c. Use of information from case-comparison study to construct a population-based study to determine the prevalence of MCS
   d. Follow-up of a defined population subjected to a discrete and sudden exposure to assess the initiation of hypersensitivity and its natural history
4. Consensus was reached among all workshop participants that challenging subjects in a well-defined environment should have the highest priority for future research

II. Association of Occupational and Environmental Clinics (AOEC) Meeting on Chemical Sensitivity, September, 1991 (AOEC, 1992).

A. Sponsor: ATSDR
B. Participants: Invited speakers representing divergent views on MCS, members of the AOEC which includes occupational medicine physicians from academia and private practice
C. Recommendations (4 groups):
   1. Group on Characterizing Patients: Proposed a case definition for research (see Table 1, Proposed Case Definitions)
   2. Group on Characterizing Events
      a. Assessment of incidence and prevalence of MCS
      b. Surveys of specific occupational cohorts and cross-cultural studies of "naive" populations, such as pesticide-exposed agricultural workers in the Third World
      c. Longitudinal studies of populations exposed in "natural" experiments such as a sick building
      d. Case registries for descriptive and future serologic studies of panels of MCS patients
      e. Double-blind, placebo-controlled challenge studies
      f. Studies to determine whether chemical exposures truly can be blinded
   3. Group on Treatment Methods
      a. A study of the effects of early intervention in an exposed population, such as critical incident counseling
      b. Randomized, controlled trials of therapies that have some reasonable theoretical basis
   4. Group on Mechanisms
      a. Challenge studies, including but not limited to chamber studies (the latter should address the issue of adaptation)
      b. Studies of olfactory function and the nasal-olfactory-limbic pathway
      c. Neuro-imaging studies including the use of pharmacologic probes
      d. Prospective studies of cohorts of persons sensitive to chemicals
      e. Studies of families of MCS patients, both medical and psychological

Based upon the many clinical observations and few studies available, a number of mechanistic hypotheses have been advanced to explain MCS. Among these hypotheses are:

1. Immune dysfunction or sensitization
2. Neurological damage or sensitization
3. Impaired detoxification pathways
4. Inflammation
5. Vasoconstriction/vasculitis
6. Psychiatric or psychological disorders, such as:
    a. An inappropriate belief that chemicals are causing illness
    b. Post–traumatic stress disorder
    c. Conditioned behavior (odor conditioning)
    d. Somatoform disorder
    e. Depression
7. Combinations of the above mechanisms

These proposed mechanisms are discussed in detail elsewhere (Cullen, 1987; Ashford and Miller, 1991; Bell et al., 1992). The first two have enjoyed the most attention by proponents of the illness. Up to now, most clinical studies of MCS patients have focused on markers of immunological, neurological, inflammatory and psychological responses (Table 5).

Clinical ecologists, a few other physicians in the private sector, and some commercial laboratories have reported alterations in a number of parameters in these patients, including T and B lymphocyte counts; helper/suppressor T cell ratios; immunoglobulin levels; autoimmune antibodies (including antinuclear, antismooth muscle, antithyroid, antiparietal cell and other autoantibodies); activated T lymphocytes (TA1 or CD26); quantitative EEGs; evoked potentials; SPECT and other brain scans; levels of various vitamins, minerals, amino acids, and detoxification enzymes; and blood or tissue levels of pesticides, solvents and other "pollutants." Flaws in these studies are many and varied, but include: Failure to define the study population (no case definition used); failure to compare cases with age- and sex-matched controls; failure to blind specimens so that those performing the analyses are unaware of whether specimens came from subjects or controls; and failure to assess the accuracy and reproducibility of the test method. For these reasons, results of studies performed by clinical ecologists or commercial laboratories have been viewed with considerable skepticism by regulatory agencies and academic researchers. Some MCS proponents claim that different immunological abnormalities occur in different patients. However, if enough tests are done, statistically a certain number will be abnormal (e.g., one in twenty). This is not always taken into account. With regard to claims of immunological dysfunction, to date no single, consistently abnormal immunological parameter has been demonstrated in these patients. This could be because there are no changes in immune system function, or because relevant cells or cytokines have not been examined, or because changes are spurious, for example, if neurological disruption led to a spectrum of immunological sequelae.

TABLE 5. Multiple Chemical Sensitivity Clinical Studies Measuring Nonneuropsychiatric Endpoints (See Table 2 in accompanying paper by I.R. Bell for results of neuropsychiatric studies)

Author(s) Date	Subject selection criteria	No. of subjects (M:F) Source	Controls? No. of subjects (M:F) Type	Chemical challenges performed? Type	Parameters measured	Major findings
Doty et al. 1988	Self-reported responses to chemicals + high score on Randolph chemical exposure questionnaire	18 (6:12) Ads in patient newsletter, physician referrals	Yes. 18 (6:12) Matched for gender, age, ethnicity, smoking + no evidence of MCS	Olfactory threshold determinations for phenylethyl alcohol, followed by methyl ethyl ketone	Physiological: Nasal airflow resistance, odor detection threshold, heart rate, BP, respiratory rate	Physiological: Subjects had significantly higher nasal resistances pre- & post-challenge than controls, higher average respiratory rate. No differences between subjects and controls for olfactory thresholds, heart rate, blood pressure
Fiedler et al. 1992	Cullen MCS criteria + good health prior to exposure + no psychiatric history	11 (3:8) Patients seen in university occupational medicine clinic	No	No	Immunological: IgG, IgA, IgM, IgE, CH50, C3, C4. Allergy skin tests (10 antigens); Delayed-type hypersensitivity skin tests (4 antigens); Delayed-type patch tests (8 antigens)	Immunological: Scattered tests out of normal lab ranges, but no significant or consistent abnormalities
Leznoff 1993	Self-reported MCS with Type A or B symptoms: A: Breathlessness & lightheadedness B: throat-related symptoms	15 (3:12) (in another 5 subjects sex not specified); Workers' Comp, disability & other referrals for allergy consultation	No	Yes. Single, unblinded challenge tailored to patient (e.g., perfume, cigarette smoke, hairspray, detergent)	Type A (15 patients): Pulmonary function, pCO_2, pO_2. Type B (5 patients): Laryngoscopy, phonograms	Type A: In 10/15 subjects symptoms were reproduced; no changes in pulmonary functions; pCO_2 fell & pO_2 rose post-challenge. Author's interpretation: hyperventilation and chemophobia. 5/15 had neither symptoms nor changes in pCO_2 or pO_2. Type B: 5/5 subjects had no symptoms or laryngoscopic changes

TABLE 5. Multiple Chemical Sensitivity Clinical Studies Measuring Nonneuropsychiatric Endpoints (Cont'd.)

Author(s) Date	Subject selection criteria	No. of subjects (M:F) Source	Controls? No. of subjects (M:F) Type	Chemical challenges performed? Type	Parameters measured	Major findings
Meggs and Cleveland 1993	Cullen MCS criteria; current smokers (2/10) included	10 (6:4) University allergy clinic referrals; self-referred	No	No	Fiberoptic rhinolaryngoscopy in 10/10; allergy skin tests in 7/10; Pulmonary function tests in 7/10; methacholine challenge in 2/10	Abnormal rhinolaryngoscopic findings in 10/10 patients including edema, excess mucus, cobblestoning, mucosal injection, blanching around vessels; + skin tests in 5/7; normal PFTs in 7/7; normal methacholine challenges where performed
Simon et al., 1993	Recorded diagnosis of MCS + ill for 3 months or longer + symptoms in CNS & at least 2 other systems + self-reported sensitivity to 4 or more of 14 common exposures	41 (6:35) Community allergy practice billing records (56% of eligibles enrolled)	34 (6:28) Musculoskeletal/back injury patients from university clinics (41% of eligibles enrolled)	No	Immunological: Blinded samples for T cells (total, CD4, CD8); B cells; CD25 (IL-2R+); CD26 (TA1, activated T cells); IL-1 generation by monocytes; autoantibodies against parietal cells, mitochondria, smooth muscle, brush border, nuclear components	Immunological: No significant differences between patients and controls; lower IL-1 generation among cases interpreted as probably due to laboratory methods
Terr 1986	Prior diagnosis by clinical ecologist of environmentally induced illness	50 (11:39) 43 = evaluations for Workers' Comp; 3 = evaluations for litigation; 4 = self or	No; laboratory normal ranges used for comparison	No	T cells (total CD4, CD8); B cells; IgG, IgA, IgM, IgE, C3, C4	T cells in normal ranges; B cells elevated in one-third; high B cells & high IgA in 4 consistent with history of infections; other tests within expected ranges

A major limitation of studies of MCS up to the present time is the fact that all but one have been performed on patients under non-exposure conditions. In order to maximize the opportunity for detecting an abnormality, it may be important to compare markers in patients before, during, and after a salient exposure. Physicians who evaluate individuals with suspected occupational asthma often have patients keep a record of their peak flow readings before, during, and after exposures at work. Some physicians perform a provocative inhalation challenge with the suspected substance. At baseline or random points in time, patients with occupational asthma may exhibit normal pulmonary function. In parallel fashion, provocative challenges may be key to detecting and diagnosing MCS.

Because adaptation could affect patients' responses, exposure challenges may need to be performed after patients have been removed from their usual background of everyday exposures, including the challenge substance itself, for a sufficient period of time that any tolerance they may have developed does not interfere with responses during testing. Again, in the case of occupational asthma it is recognized that inhalation challenges should not be conducted either too soon or too long after removal from the workplace; in the former case, tolerance may have developed, and, in the latter, sensitivity may be waning. Thus, in order to observe the most robust effect of a particular exposure, patients may need to be tested within a narrow window of time, perhaps seven to ten days after the last exposure, and in the absence of background exposures that may trigger extraneous symptoms. For this purpose, it has been proposed that patients be housed in an environmentally controlled hospital unit prior to challenges (Figure 4) (Ashford and Miller, 1991; Miller, 1992). At the conclusion of the NRC workshop on MCS, participants unanimously endorsed human challenge studies using a controlled environment, assigning this approach their highest priority for research on MCS (National Research Council, 1992).

Future research on MCS depends upon the development of a case definition for the condition. The six case definitions that have been proposed thus far differ greatly in terms of the minimum number of organ systems that must be affected (one to three); whether patients with other definable clinical or psychological conditions should be excluded; whether blinded, provocative challenges are required; and whether the illness has to have been acquired following a documented exposure (Table 6). Half of the proposed case definitions assert that symptoms in one organ system are sufficient for diagnosing the condition (Ashford/Miller, Nethercott et al., and NRC). All but two (AOEC and Cullen) agree that other definable clinical conditions, such as asthma, arthritis, vasospasm, and seizure disorder should not be excluded; the majority also agree that chemical sensitivity could be an etiology for these diagnoses, which themselves are simply descriptive clinical labels. None of the case definitions excludes psychological conditions, such as somatization disorder or depression. The AOEC and Cullen definitions exclude other clinical diagnoses, but not psychological ones; such an approach might tend to bias study populations toward those with psychological problems.

TABLE 6. Features of Proposed Research Case Definitions for MCS[1]

	Ashford/ Miller	AOEC	Clinical Ecology	Cullen	Nethercott et al.	NRC
Minimum number of organ systems that must be affected	1	3	2	2	1	1
Excludes other definable clinical conditions such as asthma, arthritis, vasospasm, seizure disorder	No	Yes	No	Yes	No	No
Excludes psychological conditions such as somatization disorder, depression	No	No	No	No	No	No
Provocative challenge required to document	Yes	No	No	No	No	No
Must be acquired in relation to a documentable environmental exposure	No	No	No	Yes	No	No

[1]Sources: Ashford and Miller, 1991; Association of Occupational and Environmental Clinics (AOEC), 1992: Clinical Ecology Journal (definition appears in each issue); Cullen, 1987; Nethercott et al., 1993; National Research Council, 1992.

The case definition proposed by Dr. Ashford and this author requires blinded, provocative challenge in a controlled environment to document chemical sensitivity. It has been our opinion that such an approach is required to define the etiology of MCS, as well as the etiology of other clinical conditions in which environmental triggers have been alleged by some, such as chronic fatigue, headaches, depression, and asthma. In our view, other case definitions prematurely exclude potential cases from study. For example, an unknown but perhaps sizeable number of patients with asthma might have bronchoconstriction and inflammation on the basis of low-level chemical exposures. We have urged that such patients not be excluded from study, and that a broader perspective be adopted, i.e., that chemical sensitivity may not be a single illness, but perhaps an etiology for multiple disorders, just as infectious agents are an etiology for meningitis, syphilis, and pneumonia which differ greatly in their clinical presentations. In other words, we have viewed chemical sensitivity as a possible new mechanism for a variety of chronic illnesses. Others argue that challenges in a controlled environment would be costly and that not everyone could be evaluated in such a specialized unit, especially given the fact that no such research facility currently is available. Finally, only one case definition requires that the condition be acquired in relation to a documentable environmental exposure (Cullen). The other definitions acknowledge that some patients report life-long illness or becoming ill following a series of less well-defined exposures over several years and recognize that such individuals may be chemically sensitive as well.

CONCLUSION

Understanding MCS is pivotal to establishing sound environmental policy. If there is a subset of the population that is especially sensitive to low-level chemical exposures, a strategy for

protecting this subset must be found. If it were to be determined that certain chemical exposures can lead to MCS, then perhaps these (sensitizing) exposures could be avoided. Perhaps by preventing chemical accidents, forbidding occupancy of buildings prior to finish-out or completion, avoiding use of cholinesterase-inhibiting pesticides indoors, etc., society could protect more vulnerable individuals from becoming sensitized in the first place. It would make little sense to regulate chemicals at the parts per billion level or lower if what was required was to keep people from becoming sensitized in the first place. Indeed, by understanding the true nature of MCS and who is at risk, we may prevent unnecessary and costly overregulation of environmental exposures in the years to come.

Chemical sensitivity could be a new paradigm that has the potential to explain many chronic and costly illnesses, including fatigue, depression, headaches, and asthma, or it could be nothing at all. Not understanding MCS, we take an immense gamble. But knowledge will not come cheaply. Future studies on chemical sensitivity that involve blinded challenges in a controlled environment, that utilize brain imaging, state-of-the-art immunological testing or other sophisticated tests, and that compare adequate numbers of patients and controls, will be costly. Funding agencies will need to invest adequate sums to acquire answers in this area as they have for other diseases, such as breast cancer and AIDS. Until sufficient research funds become available, chemical sensitivity no doubt will continue to pit physician against physician, perplex policy makers, and impoverish patients and corporations alike.

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