

GULF WAR ILLNESSES

Presidential Advisory Committee on Gulf War Veterans' Illnesses
Meeting on February 27, 1996, in San Antonio, Texas
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Thank you for the invitation to address your committee.

Over the past three years, I have served as a consultant to the Department of Veterans Affairs (DVA) Regional Referral Center for Persian Gulf War veterans in Houston, Texas. I have also served on the Department of Veterans Affairs Persian Gulf Expert Scientific Committee since its inception. I am boarded in Allergy/Immunology and Internal Medicine, and have authored or co-authored approximately 20 scientific publications on multiple chemical sensitivity or MCS.

There is a growing sense of urgency among physicians, scientists and the public about chemical sensitivity and the need to define and understand it. Several factors contribute to this sense of urgency: (1) Increasingly, private and academic physicians are reporting MCS or features of it in their patient populations; (2) MCS appears to be associated with severe and protracted disability in a large percentage of cases; (3) the societal costs of MCS in terms of lost productivity, medical bills, compensation claims and litigation are huge. Forty percent of 112 MCS patients we surveyed reported having seen ten or more health care practitioners. Eighty percent reported working full-time prior to their exposure, yet at the time of our survey (an average of seven years post-exposure), 80% said they were unable to work or could work only

part-time. The majority of MCS patients appear to be *credible* individuals--schoolteachers, mechanics, nurses, lawyers, technical staff at the Environmental Protection Agency, and soldiers with good prior work records--who report major deterioration in their health and ability to function following an identifiable exposure to chemicals.

Multiple chemical sensitivity has been attracting increasing scientific interest over the past few years. A number of federal agencies, including the National Research Council, the Agency for Toxic Substances and Disease Registry, the Environmental Protection Agency, and the National Institute of Environmental Health Sciences have sponsored workshops on MCS. In addition, a federal interagency working group on MCS has been formed. Two days ago, I returned from a World Health Organization workshop on MCS held in Berlin where clinicians and scientists from the United States, Canada and Europe formulated policy and research recommendations. Because of the current lack of scientific data on MCS, participants accorded a high priority to research. In particular, double-blind, placebo-controlled challenge studies to distinguish psychogenic from toxicogenic responses were deemed essential and urgent in order to define the nature and origins of these patients' environmental intolerances so that effective treatment, public health protection and policies can be developed and implemented.

Chemical sensitivity is a complex phenomenon that cannot be addressed adequately in the short time available today. Given the importance of this problem in the eyes of many Gulf veterans, other patients, and scientists, I hope your committee will consider devoting more time to it during a later meeting. It is one of the few mechanistic hypotheses that offers a plausible link

between the Gulf veterans' unexplained illnesses and environmental exposures.

In this presentation, I will focus on three points:

- 1) There are striking similarities between MCS and the unexplained illnesses of the Gulf War veterans.
- 2) Neither MCS nor the veterans' illnesses constitute a syndrome, nor are they explainable by any currently known mechanism for disease. However, the similar phenomenologies of both conditions suggest that a new general mechanism or theory for disease, involving chemically-induced loss of natural tolerance could be operative. This theory of disease has been called "toxin-induced loss of tolerance."
- 3) Carefully-conducted scientific studies will be needed to determine whether chemical intolerances explain the symptoms of MCS patients and/or Gulf veterans. Such research will require that double-blind, placebo-controlled challenges, using chemicals at concentrations encountered in normal daily living, be conducted while patients stay in a specially-designed hospital research unit, a so-called "Environmental Medical Unit."

Briefly, chemical sensitivity appears to entail two-steps: (1) Induction and (2) triggering. The inducing or initiating exposure may involve any of a wide variety of substances, including pesticides, solvents, indoor air contaminants, drugs, etc. It may be acute as in a chemical spill,

intermittent as in many industrial exposures, or chronic as in a sick building. *Loss of tolerance* appears to occur as a consequence of this initial exposure. Subsequently, extremely low levels of chemicals, levels that do not bother most people and were never a problem for that individual before, trigger symptoms.

The Gulf veterans' health complaints resemble those of chemical sensitivity patients when these patients *first became ill*, before they were aware of any relationship between their symptoms and exposures. In the earliest stages of their illness, chemical sensitivity patients often report flu-like symptoms that do not go away. They frequently receive a diagnosis of Chronic Fatigue Syndrome. Later, these individuals say they discover that *specific* exposures trigger their symptoms. They may not notice this until another individual or physician points this possibility out to them and they undertake a trial of avoidance and re-exposure.

In addition to their sensitivity to specific inhalants, individuals with chemical sensitivity frequently report intolerances to various medications and foods, and may also report intolerances for alcoholic beverages, caffeine or tobacco. In the early stages of their illness, they may be unaware of any specific food intolerances and may only report abdominal discomfort, bloating, diarrhea, extreme fatigue or other symptoms *after meals*. Only by testing one food at a time do MCS patients say they were able to learn which particular foods they could no longer tolerate.

In 1989, I co-authored a report on MCS for the New Jersey State Department of Health. The report identified four groups in which chemical sensitivities had been described. Industrial

workers, sick building occupants, persons living in contaminated communities and individuals with heterogeneous personal exposures to drugs, pesticides or other substances. Subsequently, we conducted a questionnaire survey on MCS. Responses of 37 persons who reported developing MCS following an organophosphate or carbamate exposure and 75 who reported onset of MCS following exposure to air contaminants associated with remodeling were compared with those of 112 age-, gender-, and education-matched controls. Later, the same questionnaire was administered to the first 59 consecutive Gulf veterans referred to the DVA's Houston Regional Referral Center for comprehensive evaluation. Eight symptoms scales were derived via factor analysis and were compared for the four groups. Striking similarities were seen, with most of the veterans' responses falling between those of the two MCS groups. Similar ordering in terms of overall severity was seen for the scales of the veterans' group and the two MCS groups.

The DVA's Houston Regional Referral Center has assumed a leadership role in recognizing the importance of obtaining comprehensive exposure histories in evaluating veterans, and in helping veterans understand the current controversies in the medical profession concerning MCS. While taking histories on more than 75 veterans I have been invited to see in Houston, I have learned that the majority report new intolerances since the Gulf War. Most patients do not routinely report such intolerances to a physician even if they have them. Generally, they will focus on describing symptoms like headache or confusion. Further, if they were to say they had trouble concentrating or felt nauseated while driving, neither they nor their physicians would be likely to entertain the notion that their symptoms might be triggered by exposure to traffic exhaust.

Physicians need to ask patients about new chemical, food and other intolerances, and not expect patients to volunteer such information.

78% of the first 59 veterans seen at the Houston Referral Center reported new-onset intolerances to various chemical inhalants. For example, former mechanics who said they used to enjoy the smell of engine exhaust and "bathe" in solvents with no associated symptoms, now report severe symptoms with these exposures since the War. In addition, 78% reported new food intolerances since the Gulf War; 40% of those who had taken medications reported one or more adverse drug reactions; 66% of those who used alcoholic beverages reported that even a small amount, e.g., 1 can of beer, made them feel ill; and 25% of those who used caffeine reported they felt ill if they drank coffee or another caffeinated beverage.

Neither MCS nor the veterans' illnesses fulfill criteria for being a syndrome, i.e., a constellation of symptoms that form a "picture" of a disease. Nor does the phenomenology of MCS or the veterans' illnesses fit that of any known medical or psychiatric disease. On the other hand, certain observations suggest that MCS and the Gulf veterans' illnesses could have an organic basis. These observations include:

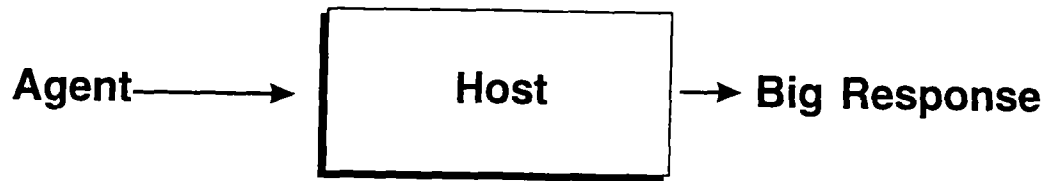
- 1) The demographic diversity of groups reporting similar symptoms and intolerances following an exposure event.
- 2) The temporal cohesiveness between onset of multiple intolerances and an exposure event.

- 3) The internal consistency in these patients' reporting not only intolerances to common airborne chemicals, but also to various foods, drugs, caffeine and alcoholic beverages.
- d) The observation that many MCS patients who have avoided problem chemicals and foods report marked improvement or resolution of their symptoms.

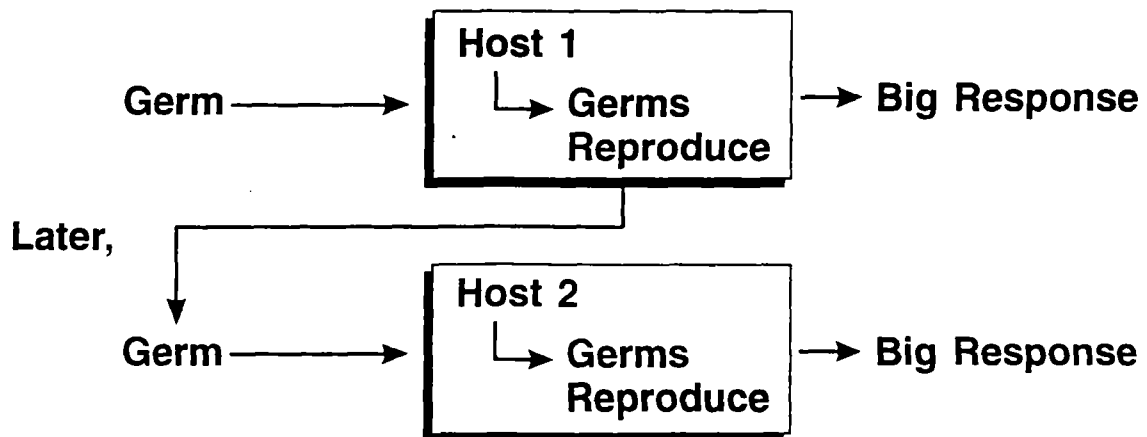
Historically, new theories of disease have arisen when physicians observed patterns of illness that did not fit accepted explanations for disease in their time, for example, the germ theory or immune theory of disease. Likewise, the illnesses under discussion here do not conform to current, accepted explanations for disease or toxicity. Objections to chemical sensitivity have included concerns that:

- 1. Too many different chemicals have been said to cause it.
- 2. Patients report too many symptoms involving any and every organ system.
- 3. No known physiological mechanism explains it.
- 4. No biomarker for it has been identified.
- 5. Total avoidance of chemicals is impractical.

Theories of disease attempt to explain what is going on inside a "black box," the patient, prior to overt illness, as illustrated below:



A theory of disease is a yet-to-be-established, general mechanism for a *class or family of diseases*. For the germ theory of disease, the boxes depicting the general mechanism of infection would look something like this:

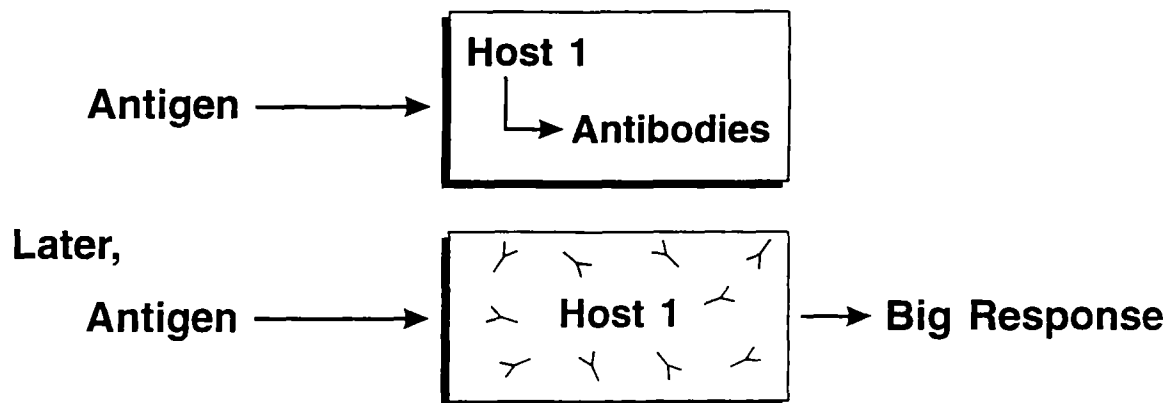


Note that:

1. Many different kinds of germs cause responses.

2. There are many different responses involving any and every organ system (pneumonia, meningitis, cellulitis, etc.)
3. *Specific* mechanisms vary greatly, for example cholera versus AIDS versus shingles.
4. There is no single biomarker; identifying specific germs took years.
5. Prevention (avoidance, antiseptics, sanitation, use of gloves) *preceded* knowledge of specific mechanisms.

For the immune theory of disease, the boxes would look like this:



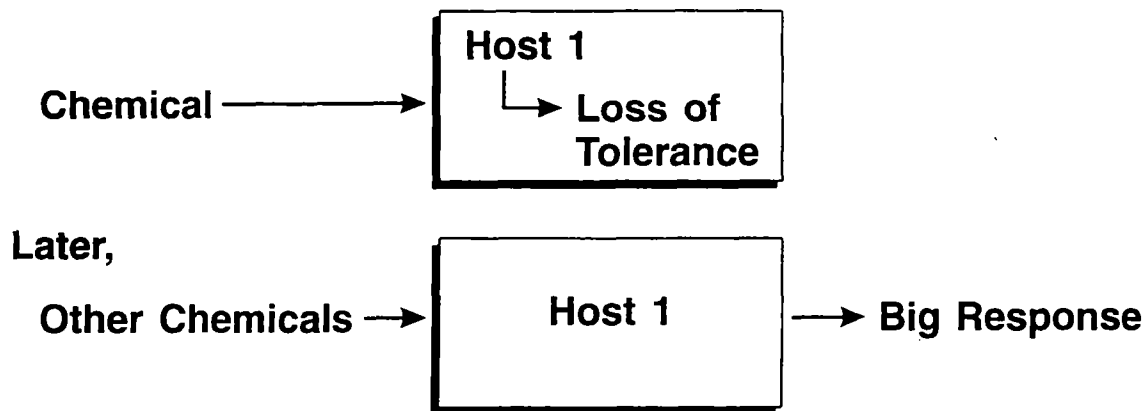
Once again, notice that:

1. Many different kinds of antigens cause responses.
2. There are many different responses involving any and every organ system (skin, respiratory, gastrointestinal, etc.)
3. *Specific* mechanisms vary greatly, for example, poison ivy versus allergic rhinitis

versus serum sickness.

4. There is no single biomarker; identification of specific antibodies took years.
5. Prevention (avoidance, allergy shots) *preceded* knowledge of specific mechanisms.

For toxin-induced loss of tolerance, the boxes might look like this:



For toxin-induced loss of tolerance, as for the germ and immune theories of disease:

1. Many different kinds of chemicals may cause responses.
2. There may be many different responses involving any and every organ system.
3. *Specific* mechanisms may vary greatly.
4. It is conceivable that there is no single biomarker for response; identification of biomarkers may take years.

5. Prevention (avoidance of initiators or triggers) may *precede* knowledge of specific mechanisms.

While the concept "loss of tolerance" may sound vague, in fact it is not. What these individuals report is a loss of *specific* tolerance to *particular* chemicals, foods, etc. Note that this theory does not exclude the possibility that toxin-induced loss of tolerance could turn out to be a special case of the immune theory of disease, just as allergy or delayed-type hypersensitivity are special cases that fall under the general classification of immunological disorders. One consequence of viewing toxin-induced loss of tolerance as a theory of disease is a shift in perspective from chemical sensitivity as a possible syndrome to chemical sensitivity, or now toxin-induced loss of tolerance, as a *class* of disorders, parallel to infectious diseases or immunologic diseases. Much effort has been devoted to developing a case definition both for chemical sensitivity and for the Gulf veterans' illnesses, with a singular lack of success. This lack of success would not be surprising if in fact these illnesses represented a new class or family of disorders. Certainly, it would not be feasible to develop a single clinical case definition that would embrace *all* infectious diseases.

New theories for disease that withstand scientific scrutiny come along infrequently. The past century has witnessed the inculcation of the germ and immune theories of disease into medical practice. Equating toxin-induced loss of tolerance to either one of these theories, both of which have been widely corroborated, would be premature and presumptuous. At the same time, toxin-induced loss of tolerance does have many of the earmarks of an *emerging* theory of

disease, including the vituperative professional disputes which surround it.

What is plausible depends upon the biological knowledge of the time. Two-thirds of the 660,000 deaths during the Civil War were caused by infections. However, military physicians at that time had no concept of microbes or infectious diseases. Cases with fevers were divided into three categories: Remittent, intermittent and relapsing. Unrelated diseases likely were assigned to those categories, for example, typhus, typhoid, malaria, abscesses, tuberculosis, leptospirosis, borrelia, pneumonia, influenza, and infectious diarrhea. Civil War surgeons commonly attributed disease to toxic miasma or "effluvia" from the swamps or to inadequate ventilation in the tents. Only a few years after the Civil War, a series of discoveries led to the development of the germ theory of disease. It is conceivable that medical understanding of chemically-induced disorders today is only beginning to develop and that MCS and the Gulf veterans' unexplained illnesses are some of the first evidence that current explanations for disease are not sufficient and that a new theory of disease is about to emerge.

Once chemically sensitive individuals become ill, because their sensitivities appear to spread to a multitude of common exposures, it may be important for them to be removed both from the original exposure and from other chemicals that now may trigger adverse symptoms. Sorting out which exposures are perpetuating the illness may be very difficult: Environmental chemical exposures are ubiquitous; their resultant symptoms may overlap in time; and to some degree individuals adapt as exposure continues. Urgently needed is a clinical approach for determining whether chemical intolerances are at the root of these patients' problems. There is a growing

consensus that important questions concerning causation cannot be answered without appropriate studies in a controlled environment or Environmental Medical Unit--a hospital environment in which chemical exposures have been reduced to the lowest levels practicable via specialized air filtration and the use of construction materials and furnishings that do not release chemicals into the air. There, in accordance with scientific protocols, patients could be removed from their usual home and workplace exposures to see if they improve, and, if they do, be re-exposed to very low levels of common chemicals to see whether their symptoms recur. For research purposes such testing should be conducted in a double-blind, placebo-controlled manner.

Availability of an EMU would allow physicians to refer a wide variety of cases in which environmental sensitivities were suspected to the unit for more definitive evaluation. There, physicians could observe first-hand whether a sick patient's symptoms improved after several days on a special diet in a clean environment. If improvement occurred, single chemicals at concentrations encountered in normal daily living and single foods could be re-introduced, one at a time, while the effects of each introduction were observed. Thus, the EMU would serve as a tool for ruling in or ruling out environmental sensitivities in the most direct and definitive manner possible. Studying complicated patients like chronic fatigue sufferers or ill Gulf War veterans in a conventional exposure chamber would provide none of the same information since chambers allow only short-term residence, do not control the entire range of background contaminants for sufficient periods, and provide inadequate separation from background exposures prior to challenges.

An analogy illustrates the importance of controlling exposures for extended periods prior to challenge: If one wished to determine whether headaches in a coffee drinker with a 10- to 15-cup-per-day habit were due to caffeine, it would not work simply to give the person a cup of coffee and ask him how he felt. It is intuitively obvious that the individual would need to stop using caffeine for a while before a meaningful test of caffeine sensitivity could be performed. In this instance, a false negative challenge would be the most likely consequence of failure to avoid coffee prior to challenge. Similarly, placing a putatively sensitive person in a conventional exposure chamber and exposing him to a few parts per million of a chemical might not produce any noticeable any effect. On the other hand, if he were to remain in a clean environment (EMU) for a few days before being tested *and* his condition improved, one could then perform meaningful challenges.

This approach to research (blinded challenges in a controlled environment) was recommended by physicians and researchers attending two national workshops on chemical sensitivity--one organized by the National Academy of Sciences and the other by the Agency for Toxic Substances and Disease Registry. Without carefully-conducted challenge studies of this kind, questions concerning etiology (i.e., toxicogenic versus psychogenic) cannot be resolved.

Although research in such an environmental unit has been proposed to DOD, DVA and NIEHS, studies of this nature have not yet been funded. While Congress authorized partial funding for such a project and DOD agreed to provide the remainder, an Environmental Medical Unit still has not been constructed.

In summary, the illnesses of MCS patients and Gulf veterans share much in common: Similar kinds of symptoms and loss of natural tolerance for chemicals, foods and drugs following an "exposure event." Their illnesses point to a possible new general mechanism or theory of disease, described as "toxin-induced loss of tolerance." Confirmation or refutation of this theory rests upon double-blind, placebo-controlled challenges conducted in an Environmental Medical Unit.

**Committee on Government Reform and Oversight
Subcommittee on Human Resources and Intergovernmental Relations
United States House of Representatives**

Invited Testimony by

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September 19, 1996

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Good afternoon. I was invited here by your subcommittee to address the question, "Could low levels of an organophosphate like the nerve agent Sarin be responsible for some of the chronic health problems reported by Gulf War veterans?" Of course, Sarin was not the only organophosphate-type exposure soldiers may have encountered in the Gulf: Pesticides in this chemical class and pyridostigmine bromide, a related carbamate drug, were also widely used.

Effects of low level chemical exposures have been the focus of my research for the past eight years. I co-authored a report for the New Jersey State Department of Health (Ashford and Miller, 1989) and a subsequent book (Ashford and Miller, 1991) about patients who report developing chronic illnesses and chemical intolerances following exposure to various chemicals, including pesticides, solvents, and combustion products. Some of the sickest individuals we have studied, as a group, seem to be those who were exposed to an organophosphate or carbamate pesticide. In 1995, we published a study of 37 patients who had been exposed to pesticides in this class and who subsequently reported developing multi-system symptoms and new-onset chemical, food and drug intolerances (Miller and Mitzel, 1995). Eighty percent of these individuals told us they were no longer able to work or could only work part-time because of their health problems. The most common symptoms reported by these individuals at the time they were exposed were often flu-like, for example, fatigue, concentration difficulties, headaches, shortness of breath, musculoskeletal pain and gastrointestinal symptoms (Table 1). In general, these individuals did not report the classical symptoms of organophosphate poisoning. However, they did report developing new and unusual intolerances for common chemicals such as fragrances, traffic exhaust, gasoline, and household cleaning products. In addition, many found they could no longer tolerate alcoholic beverages, various foods, caffeine, and medications they were prescribed, including antidepressants.

Four years ago the Chief of Staff of the Houston VA Medical Center asked me to consult on the first Gulf veteran admitted to their newly-designated Regional Referral Center for Gulf War Veterans. Since then, I have been asked to evaluate about 75 Gulf veterans. These

veterans' symptoms and their frequent reports of new-onset intolerances to chemicals, foods and medications reminded me of the civilians we had studied with histories of exposure to organophosphate or carbamate pesticides or to mixtures of solvents at low levels.

Comparison of eight symptom scales derived by factor analysis revealed similar ordering of symptoms in the Gulf veterans and the pesticide-exposed civilians (Figure 1). All of the civilians reported new chemical intolerances because they were selected for our study on this basis. Notably, seventy-eight percent of the first 59 consecutive Gulf veterans seen at the Houston Referral Center also reported new-onset chemical intolerances since the War. For example, mechanics who once liked the smell of engine exhaust or said they used to "bathe" in solvents with no associated symptoms, reported severe symptoms with these exposures since the War. One mechanic told me that before the War his idea of the perfect perfume was WD-40. Now WD-40 and many other low level chemical exposures make him feel ill. Seventy-eight percent of the veterans also reported new food intolerances or feeling ill after meals; 40% had experienced one or more adverse reactions to medications since the War; 66% of those who used alcoholic beverages reported that even a small amount, such as one can of beer, made them feel ill; 25% of those who used caffeine reported feeling ill if they drank coffee or another caffeinated beverage; and 74% of those who smoked reported that smoking an extra cigarette or borrowing someone else's stronger brand made them feel ill (Table 2). More than half of the Gulf veterans reported intolerances in all three categories--chemical inhalants, foods, and drugs or food/drug combinations (Figure 2).

Most patients will not report such intolerances to their physicians. Generally, they will focus on describing their symptoms, such as headaches or irritability. Even if they were to tell their physicians that they were experiencing confusion or nausea while driving, it is unlikely that either they or their doctors would entertain the notion that their symptoms might be triggered by exposure to traffic exhaust.

There are now several studies, in addition to our own, linking chronic, multi-system symptoms to organophosphate/carbamate exposure. These agents have been implicated in similar illnesses and intolerances in pesticide-exposed casino workers (Cone and Sult, 1992), an attorney whose home was exterminated (Rosenthal and Cameron, 1991), and other persons exposed to organophosphates (Sherman, 1995). A recent European study involving nine countries revealed other cases of new-onset intolerances following exposure to various pesticides (Ashford et al, 1994). Thirty years ago, Tabershaw and Cooper (1966) described a group of agricultural workers with acute organophosphate pesticide poisoning, some of whom developed persistent symptoms. Following their acute exposure, nearly 20% reported that even a "whiff" of pesticide made them feel ill. A number of the workers quit working with agricultural chemicals for this reason. In 1961 Spiegelberg described persistent, multi-system symptoms among Germans who had worked in chemical weapons production during World War II. Notably, he also described new-onset intolerances for alcohol, nicotine and medications among these workers (Spiegelberg, 1961).

Thus there is accumulating evidence linking organophosphate-type compounds with chronic illness and new-onset intolerances in a subset of exposed persons. This unusual symptom of new-onset chemical, food, and drug intolerances appears to be a unifying theme. It would be difficult to imagine that so many people with identifiable chemical exposures would invent such a bizarre complaint. Many of these individuals now avoid fragrances they once enjoyed; no longer fill up their own gas tank or drive where there is heavy traffic exhaust because they feel ill if they do; and have given up formerly favorite foods such as pizza or chocolate because they feel sick when they eat them.

Taken together, these observations by our own group and by other researchers suggest that we may be dealing with an entirely new mechanism for disease, one we have nicknamed "Toxicant-induced Loss of Tolerance" or "TILT." A yet-to be proven mechanism of disease is a theory of disease. Hence, we have dubbed this the "TILT Theory of Disease" (Miller, 1996; Miller, in press). TILT appears to involve two steps, initiation and triggering (Figure 3): (1) After a single acute or multiple low level exposures to a pesticide, solvent or other chemical, a *subset* of those exposed appear to lose their prior, natural tolerance for a variety of common exposures such as tobacco smoke, fragrances, engine exhaust, and gasoline; (2) Following initiation, very low levels of many common substances *trigger* symptoms, including not only chemicals, but also various foods, medications, alcoholic beverages and caffeine. Symptoms generally involve multiple organ systems and wax and wane in a seemingly unpredictable manner.

Ironically, patients may be completely unaware of these intolerances because of a phenomenon called "masking": If an individual were intolerant of multiple chemicals, foods and drugs and were exposed to these substances one after another during the day, then that person's responses to these exposures might overlap in time. At any given point in time that person might feel ill but be unable to tell which exposure was triggering symptoms. In effect, there would be so much background noise that the signal was hidden. This is what is meant by "masking."

To determine whether the Gulf veterans' current health problems are now being triggered and thus perpetuated by everyday chemical exposures, physicians need to be able to minimize background chemical noise, or "unmask" their patients. Physicians and researchers attending two federally-sponsored workshops on the health effects of low level chemical exposures have recommended that double-blind, placebo-controlled testing of patients in an environmentally-controlled hospital ward be conducted in order to determine whether such low level intolerances do in fact occur (National Research Council, 1992; Association of Occupational and Environmental Clinics, 1992). To accomplish this, use of an Environmental Medical Unit has been proposed. This is a hospital unit in which chemical exposures can be controlled to the lowest levels practicable via air filtration and use of construction materials and furnishings that do not outgas (release low levels of chemicals into the air).

An analogy will help illustrate the need for such a facility. Suppose we wanted to determine

whether headaches in a coffee drinker were due to caffeine. It wouldn't tell us much if we were to simply have this person drink a cup of coffee and tell us how he felt. We would first need to have the person stop *all* caffeine for about a week. If he experienced withdrawal symptoms--headache, fatigue, irritability--that would be a hint that caffeine could be a problem for him. If his symptoms resolved after a week of avoiding all caffeine, that would provide further evidence. Then, *once his symptoms had cleared*, we could give him a cup of coffee and see how it made him feel. Failure to have this patient at a clean, caffeine-free baseline prior to challenge would likely result in a false negative caffeine challenge. By analogy, placing ill Gulf veterans in a conventional exposure chamber and exposing them to a few parts per million of some chemicals may produce misleading results. On the other hand, if they were to remain in an Environmental Medical Unit for a few days beforehand and their symptoms resolved, one could then test them to determine which exposures were triggering their symptoms.

Without carefully conducted studies of this kind, questions concerning the role of ongoing low level exposures in perpetuating the veterans' symptoms are unlikely to be resolved. Although research using an Environmental Medical Unit has been proposed to the Department of Defense, Department of Veterans Affairs and the National Institute of Environmental Health Sciences (NIH), studies of this kind have not yet been funded. While Congress authorized partial funding for such a project two years ago and the Department of Defense agreed to provide the remaining sum, an Environmental Medical Unit still has not been constructed. Until this tool is made available to physicians, Gulf veterans are likely to remain in their current Catch-22 of being required to show objective evidence of their disability and having no means by which to do so.

In summary, the illnesses of many Gulf veterans and civilians exposed to organophosphates and other chemicals share a strikingly similar pattern: Multi-system symptoms that wax and wane and loss of prior tolerance for chemicals, foods and drugs. This pattern appearing in different, chemically-exposed groups of patients provides evidence, albeit circumstantial, for an emerging new theory of disease described as Toxicant-induced Loss of Tolerance. Confirmation or refutation of this theory rests upon careful evaluation of patients in an Environmental Medical Unit. Results of studies in an Environmental Medical Unit would benefit not only those patients admitted to the Unit, but also other veterans and civilians by helping to elucidate mechanisms. Scientific understanding of these mechanisms can be expected to lead to more effective treatments and prevention.

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**Table 1. Most Common Acute Symptoms Reported by 37
Civilians Following Exposure to an
Organophosphate or Carbamate Pesticide**

<u>Symptom Category</u>	<u>Number</u>
Breathing difficulties	15
Fatigue/weakness	12
Headache	12
Agitation, trembling, irritability	12
Nausea, vomiting	11
Confusion, disorientation, trouble concentrating	10
Eye/vision problems	10
Dizziness, lightheadedness	9
Joint/muscle pain, stiffness	7
Heart racing or irregular beats	7
Diarrhea	6
Skin problems	6
Numbness or tingling	5

Table 2.

**New Onset Intolerances Reported by Gulf War Veterans (n=59)
Seen at the Houston VAMC Regional Referral Center**

	<u>%</u>
Chemical inhalants	78.0%
Medications	40.4% of those who took drugs
Alcoholic beverages	65.9% of alcohol users
Caffeine	25.0% of caffeine users
Foods	78.0%
Specific Foods	64.4%
Illness after meals	49.2%
Tobacco use	74.1% of tobacco users

Comparison of Symptom Severity

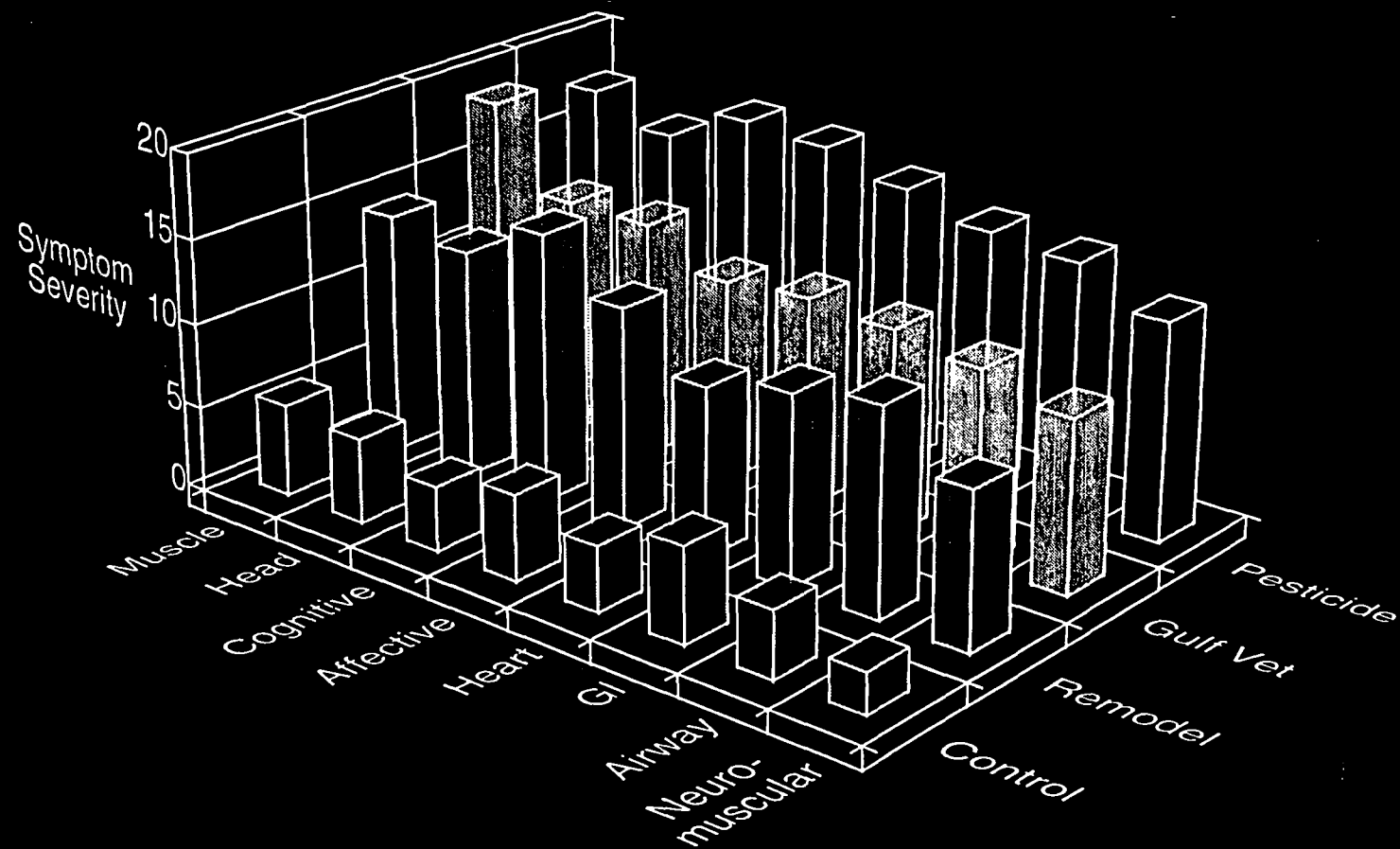


Figure 1

New-Onset Intolerances Reported by 59 Consecutive Gulf Veterans

Intolerances: $n = 52$
No Intolerances: $n = 7$

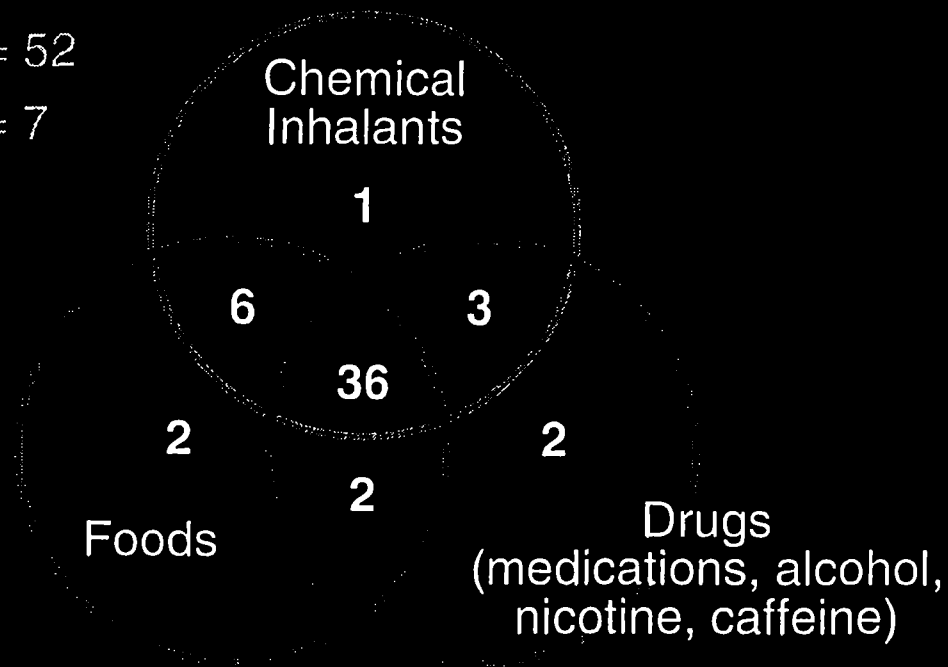


Figure 2

Phenomenology of Toxicant-induced Loss of Tolerance

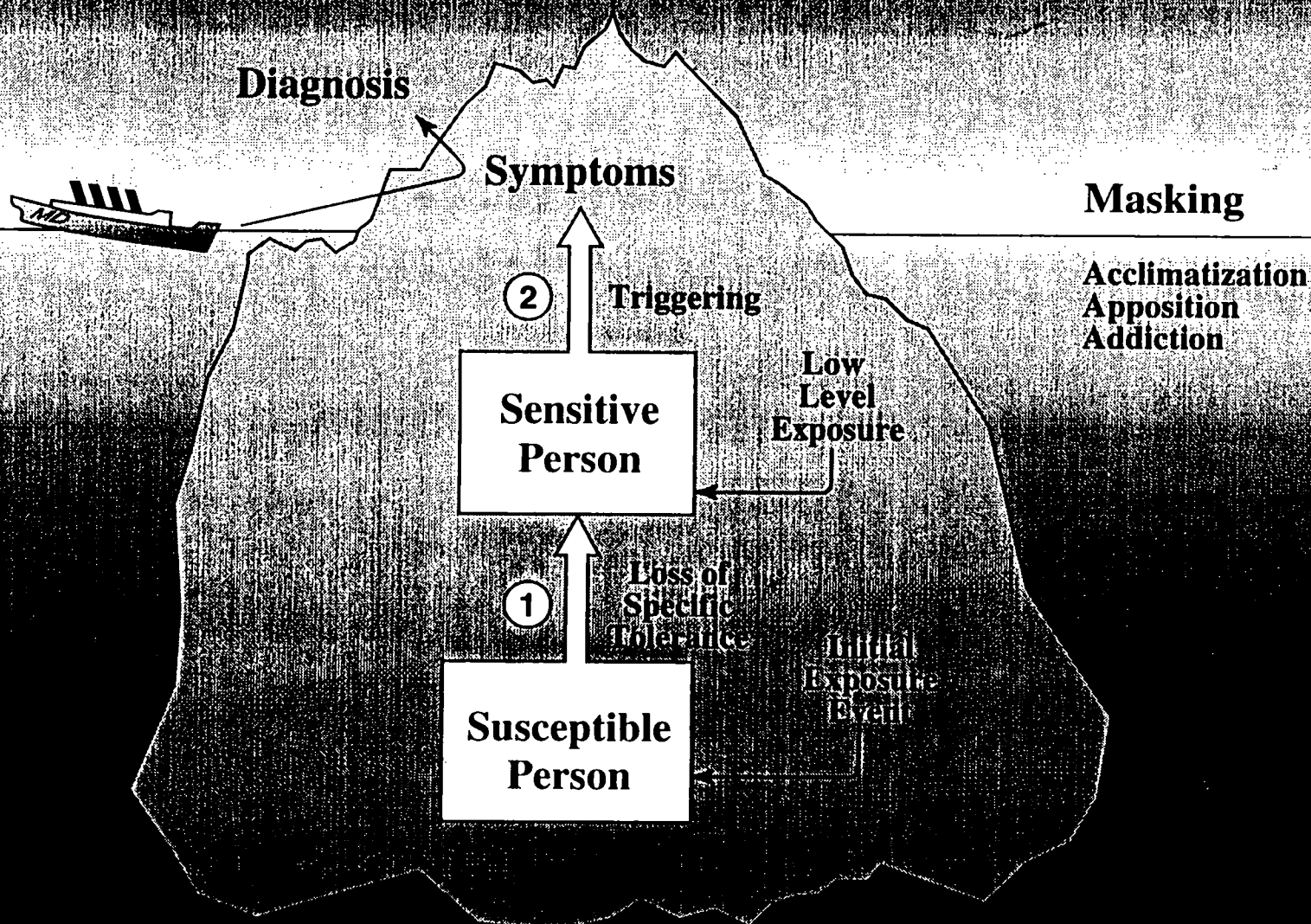


Figure 3

MULTIPLE CHEMICAL SENSITIVITY AND THE GULF WAR VETERANS

Growing numbers of Gulf War veterans have received a diagnosis of Multiple Chemical Sensitivity (MCS) or have been told their condition resembles MCS. Patients with MCS report multi-system and often disabling symptoms when they are exposed to common environmental chemicals, such as perfume, tobacco smoke, diesel exhaust, fresh paint, and new carpeting. Many of these individuals say they first became ill following an acute exposure to chemicals, for example, a chemical spill or pesticide application. Others say they gradually became ill as a consequence of repeated, daily exposure to chemicals, for example, while working in a "sick" building or living in a newly built or remodeled home. The prevalence of MCS in the general population is unknown. There is no widely accepted case definition, no uniform biological marker, and no identified mechanism for the condition. Yet Multiple Chemical Sensitivity has been the focus of three federally-sponsored professional meetings in the past three years; at least five case definitions for research on the condition have been proposed; and approximately twenty MCS patient newsletters are in circulation, some with several thousand subscribers.

There is a growing sense of urgency among physicians, scientists and the public about this condition and the need to define and understand it. Several factors contribute to this sense of urgency: (1) Increasingly, private and academic physicians are reporting MCS or features of it in their patient populations; (2) MCS appears to be associated with severe and protracted disability in a large percentage of cases; (3) the societal costs of MCS in terms of lost productivity, medical bills, compensation claims and litigation are huge. Forty percent of 112 MCS patients we surveyed reported having seen ten or more health care practitioners. Eighty percent reported working full-time prior to their exposure, yet at the time of our survey (an average of seven years post-exposure), 80% said they were unable to work or could work only part-time. The majority of MCS patients appear to be *credible* individuals--schoolteachers, mechanics, nurses, lawyers, EPA technical staff, and soldiers with good prior work records--who report major deterioration in their health and ability to function following an identifiable exposure to chemicals.

Chemical sensitivity has been reported in several different demographic groups (Table 1): (1) Industrial workers; (2) occupants of sick buildings, including office workers and school children; (3) residents of communities whose air or water has been contaminated by chemicals; and (4) individuals who have experienced personal and unique exposures to various chemicals in domestic indoor air, pesticides, drugs or consumer products. These four groups differ greatly in terms of professional and educational attainment, age and sex, and the type and levels of chemicals to which they initially were exposed. Nevertheless, all complain of multiple symptoms involving multiple organ systems. Central nervous system symptoms such as fatigue, difficulty concentrating, depression and irritability are common. Despite the demographic differences among these groups, they all share in common an initial exposure to chemicals preceding onset of their illness. The fact that a similar pattern of illness, including cognitive difficulties, mood alterations, multi-system symptoms and an unusual feature--new onset chemical, food, alcohol and/or drug intolerances--has appeared in each of these four, demographically diverse groups helps point to the possible existence of a real problem.

Like an allergy (although it does not seem to involve IgE antibodies), chemical sensitivity appears to develop in two phases: (1) Induction or sensitization, and (2) triggering. Sensitization may occur following a single, acute exposure or repeated, lower level exposures to any of a wide range of substances,

TABLE 1. CHEMICALLY SENSITIVE GROUPS (Ashford NA and Miller CS, Chemical Exposures: Low Levels and High Stakes. Van Nostrand Reinhold, 1991)

<u>GROUP</u>	<u>NATURE OF EXPOSURE</u>	<u>DEMOGRAPHICS</u>
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; schoolchildren
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	80% females; majority in 30 to 50 year age range; white, middle to upper middle class and professionals

for example, solvents, pesticides or combustion products. Once sensitization has occurred, extremely low levels of the sensitizing agent or other *structurally-unrelated* chemicals appear to trigger a wide range of symptoms. Symptoms vary greatly from individual to individual but seem to be reproducible for a single individual given a particular exposure.

The Gulf veterans' health complaints resemble those of chemical sensitivity patients when these patients *first became ill* and before they were aware of any relationship between their symptoms and exposures. In the earliest stages of their illness, chemical sensitivity patients often report flu-like symptoms that do not seem to go away. They frequently receive a diagnosis of Chronic Fatigue Syndrome. Later, these individuals say they discover that *specific* exposures are triggering their symptoms. They may not notice this until another individual or physician points this possibility out to them and they undertake a trial of avoidance and re-exposure.

In addition to their sensitivity to specific inhalants, individuals with chemical sensitivity frequently report intolerances to various medications and foods, and may also report a loss of capacity for or intolerance for alcoholic beverages, caffeine or tobacco. In the early stages of their illness, these individuals may be unaware of any specific food intolerances and may instead report abdominal discomfort, bloating, diarrhea, extreme fatigue or other symptoms *after meals*. Only by testing one food at a time do MCS patients say they are able to determine which foods they no longer tolerate.

Although there are no specific diagnostic markers or laboratory tests, nor any generally accepted case definition for MCS, it must be remembered that the same was once true of other medical conditions, such as lupus and multiple sclerosis. Several studies suggest that patients with chemical sensitivities manifest more depression than matched controls. However, it is not known (1) whether depression is the cause

of their condition, (2) whether depression in these individuals is a consequence of their having a disabling medical condition, or (3) whether depression is a symptom caused by exposure to chemicals. For example, it is known that solvent-exposed workers are at increased risk for developing both depression and memory difficulties. Possible *organic* causes for psychiatric symptoms must be ruled out before psychogenic ones are invoked.

It has been hypothesized that chemical sensitivity could involve damage to the nervous system or the immune system. To date, no single immunologic abnormality has been identified consistently in these patients. Sensitization of olfactory-limbic pathways in the brain is an intriguing mechanistic hypothesis for MCS which was the subject of a conference earlier this month (April 6-7, 1994) sponsored by the Agency for Toxic Substances and Disease Registry (ATSDR). The olfactory nerves provide the most direct link between the outside chemical environment and the brain. There is no blood-brain barrier where these nerves enter the brain as there is for other portions of the brain. The olfactory nerves communicate directly with the limbic portion of the brain, the so-called "primitive smell brain." This brain area is essential for laying down new memories (hippocampus) and regulates mood (amygdala). In addition, it supplies much of the input to the hypothalamus, which in turn regulates autonomic nervous system and endocrine function. Temperature regulation, smooth muscle tone and appetitive behaviors are influenced by hypothalamic output. For many chemically sensitive patients and Gulf veterans, mood and memory difficulties are their most disabling symptoms. The possibility exists that such symptoms could be triggered by extraordinarily low level chemical exposures and that sensitivity could spread to chemically unrelated substances as a consequence of limbic sensitization or partial kindling.

Once chemically sensitive individuals become ill, because their sensitivities appear to spread to a multitude of common exposures, it may be important for them to be removed both from the original exposure and from other chemicals that now may trigger adverse symptoms. Sorting out which exposures are perpetuating the illness may be very difficult: Environmental chemical exposures are ubiquitous; their resultant symptoms may overlap in time; and to some degree individuals adapt as exposure continues. Urgently needed is a clinical approach for determining whether or not chemical sensitization is at the root of these patients' problems. There is a growing consensus among experts, including skeptics, that these questions cannot be answered without appropriate studies in a controlled environment or Environmental Medical Unit--a hospital environment in which chemical exposures have been reduced to the lowest levels feasible via specialized air filtration and the use of construction materials and furnishings that do not release chemicals into the air. There, in accordance with scientific protocols, patients can be removed from their usual home and workplace exposures to see if they improve, and, if they do, be re-exposed to very low levels of common chemicals to see whether their symptoms recur. For research purposes such testing should be conducted in a double-blind, placebo-controlled manner.

This approach to research (blinded challenges in a controlled environment) was recommended by physicians and researchers attending two national workshops on chemical sensitivity--one organized by the National Academy of Sciences and the other by the Agency for Toxic Substances and Disease Registry. Without carefully-conducted challenge studies of this kind, questions concerning etiology (i.e., physiological versus psychological) cannot be resolved. Chemical sensitivity differs significantly from other diagnoses under consideration for the Gulf veterans' illnesses, such as Chronic Fatigue Syndrome, depression, and fibromyalgia: Chemical sensitivity is an *etiologic* diagnosis. Most other medical diagnoses, with the exception of infectious diseases, are based primarily upon patterns of signs and symptoms observed by physicians. Chemical sensitivity posits that chemical exposures may sensitize certain individuals and that their symptoms may be perpetuated by every day, low level chemical exposures. Thus, MCS offers a plausible and testable hypothesis concerning the origins of the Gulf veterans' illnesses.

GULF VETERANS VS. MCS PATIENTS (ORGANOPHOSPHATE AND REMODELING-EXPOSED) VS. CONTROLS: MEAN SYMPTOM SEVERITY

*** = Among top 20 (out of 114 possible) symptoms in Gulf veterans
and MCS-OP and MCS-RE groups**

0 = none 1 = mild 2 = moderate 3 = severe

<u>Symptom</u>	<u>PG Vets n=30</u>	<u>MCS-OP n=37</u>	<u>MCS-RE n=75</u>	<u>Controls n=112</u>
*1. Joint pain	2.6	1.9	1.8	0.9
*2. Fatigue > 6 mo.	2.5	2.4	2.1	0.3
*3. Tired	2.4	2.5	2.4	1.0
*4. Muscle aches	2.2	2.0	1.8	0.6
*5. Loss of motivation	2.2	2.1	1.8	0.9
6. Diarrhea	2.1	1.5	1.1	0.4
*7. Memory difficulties	2.1	2.3	2.1	0.7
8. Stiffness	1.9	1.8	1.4	0.7
*9. Headache	1.8	1.9	1.7	0.9
10. Tingling fingers/toes	1.8	1.9	1.1	0.5
*11. Difficulty concentrating	1.7	2.3	2.2	0.6
12. Chest pain	1.7	2.0	1.2	0.3
*13. Groggy	1.7	2.1	1.9	0.4
*14. Tense	1.6	2.1	1.6	0.8
15. Abdominal pain	1.6	1.8	1.3	0.5
16. Frequent urination	1.6	1.5	1.2	0.6
17. Weak arms	1.6	1.9	1.4	0.3
*18. Dizziness	1.5	2.2	1.8	0.5
*19. Irritable	1.5	2.0	1.8	0.7
*20. Shortness of breath	1.5	2.1	1.6	0.3
21. Depression	1.5	2.2	1.8	0.9
22. Numbness	1.4	1.8	1.0	0.3
23. Recurrent infections	1.4	1.6	1.2	0.4
24. Constipation	1.4	0.7	0.8	0.5
25. Problems focusing eyes	1.4	2.0	1.3	0.7

**SYMPTOMS RATED AS "SEVERE" BY 25% OR MORE OF GULF VETERANS
FREQUENCIES COMPARED WITH MCS PATIENTS (ORGANOPHOSPHATE AND
REMODELING-EXPOSED) AND CONTROLS**

<u>Symptom</u>	<u>%PG Vets n=30</u>	<u>%MCS-OP n=37</u>	<u>%MCS-RE n=75</u>	<u>%Controls n=112</u>
1. Fatigue > 6 mo.	76.7	67.6	52.0	2.7
2. Joint pain	70.0	43.2	38.7	3.6
3. Tired	63.3	62.2	69.3	6.3
4. Loss of motivation	53.3	43.2	34.7	7.1
5. Muscle aches	50.0	48.6	36.0	1.8
6. Memory difficulties	43.3	56.8	37.3	5.4
7. Diarrhea	40.0	27.0	12.0	0.0
8. Headache	40.0	37.8	30.7	4.5
9. Abdominal pain	36.7	27.0	21.3	2.7
10. Stiffness	36.7	27.0	18.7	1.8
11. Tingling fingers/toes	33.3	43.2	14.7	0.9
12. Concentration difficulties	30.0	54.1	42.7	2.7
13. Frequent urination	30.0	18.9	17.3	0.9
14. Recurrent infections	30.0	37.8	37.0	0.0
15. Numbness	30.0	40.5	13.3	0.9
16. Weak arms	30.0	37.8	28.0	0.0
17. Weight gain	30.0	35.1	14.7	14.3
18. Chest pain	26.7	43.2	21.3	1.8
19. Muscle cramping	26.7	24.3	14.7	2.7
20. Depression	26.7	48.6	33.3	6.3
21. Problems focusing eyes	26.7	48.6	18.7	4.5
22. Groggy	26.7	37.8	38.7	0.0
23. Nausea	26.7	18.9	26.7	0.0
24. Weight loss	26.7	21.6	17.3	1.8

OP VS. REMODEL VS. CONTROLS
EXPOSURES REPORTED AS CAUSING ILLNESS (OUT OF 98 EXPOSURES)

	<u>%OP</u> <u>(n=37)</u>	<u>%Remodel</u> <u>(n=75)</u>	<u>%Control</u> <u>(n=112)</u>
Insecticide	100	84	21
* Nail polish remover	97	92	15
Insect repellent	97	80	8
* Perfume	95	95	29
* RR deodorizer	95	89	13
Cigarette smoke	95	81	38
Hair permanent	95	68	19
* Poorly ventilated mtg. room	92	93	25
Latex paint	92	77	11
* New carpeting	89	97	7
* Fresh newspaper	89	93	10
* Detergent aisle	89	92	11
* Diesel exhaust	89	92	29
* Oil paint	89	85	6
Gasoline	89	84	14
Cigar smoke	89	80	36
Large cities	89	80	15
* New auto interior	86	96	4
* Traffic exhaust	86	91	18
* Fabric store	86	89	12

* = Among 20 exposures most frequently cited by both OP and RE groups

OP VS. REMODEL VS. CONTROLS
INGESTANTS REPORTED AS CAUSING ILLNESS (OUT OF 46 INGESTANTS)

	<u>%OP</u> <u>(n=37)</u>	<u>%Remodel</u> <u>(n=75)</u>	<u>%Control</u> <u>(n=112)</u>
* Chlorinated water	65	51	2
* MSG	62	48	22
* Milk	59	48	18
* Pizza	49	36	4
* Cheese	49	33	5
* Food dyes	46	37	1
* Chocolate	46	36	7
* White wine	46	35	11
* Cola	46	32	4
* Bread	43	43	0
* Red wine	43	41	13
* Toothpaste	43	40	1
* Beer	41	32	6
* Wheat	41	32	1
Corn	41	31	0
Corn sugar	41	29	1
Cane sugar	41	23	1
Grapes	38	32	0
Coffee	38	31	11
Candy	38	29	2

* = Among 15 ingestants most frequently cited by both OP and RE groups

**GULF VETERANS SEEN AT HOUSTON VAMC
REGIONAL REFERRAL CENTER
(n=35)**

Since the Gulf War:

- 71% (25/35) report new onset **chemical** (odor) intolerances
Most common include diesel exhaust, solvents, gasoline,
tobacco smoke, hairspray, fragrances

- 66% (23/35) report new onset **food** intolerances or feeling ill
after meals

- 46% (16/35) report new onset **drug/medication** intolerances

- 18% (6/33) who use caffeine report new onset **caffeine**
intolerance

- 65% (13/20) of those who drink report new onset intolerance
for **alcohol**

- 67% (10/15) of smokers report new onset **tobacco** intolerance

- 77% (27/35) report new onset intolerances in **two or more** of
above categories

Chemical sensitivity: symptom, syndrome or mechanism for disease?¹

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Abstract

Several different meanings have been attached to the term “chemical sensitivity” by those who use it. Feeling ill from odors is a *symptom* reported by approximately one-third of the population. The *syndrome* of chemical sensitivity, frequently called “Multiple Chemical Sensitivity” or “MCS” has been the subject of three federally-sponsored workshops; at least five different case definitions for research on MCS have been proposed. In contrast, the hypothesis that chemical sensitivity may be a *mechanism for disease* posits that a broad spectrum of “recognized” chronic illnesses, ranging from asthma and migraine to depression and chronic fatigue, may be the consequence of environmental chemical exposures. According to this theory, a two-step process occurs: (1) an initial salient exposure event(s) (for example, a one-time, intermittent, or continuous exposure to pesticides, solvents, or air contaminants in a sick building) interacts with a susceptible individual, causing loss of tolerance for everyday, low level chemical inhalants (car exhaust, fragrances, cleaning agents), as well as for foods, drugs, alcohol, and caffeine; (2) thereafter, such common, formerly well-tolerated substances trigger symptoms, thus perpetuating illness. “Masking” (acclimatization, apposition, and addiction) may hide these exposure-symptom relationships, thus obfuscating the environmental etiology of the illness. Accumulating clinical observations lend credence to a view of chemical sensitivity as an emerging theory of disease causation and underscore the need for its testing in a rational, scientific manner. While chemical sensitivity may be the consequence of chemical exposure, the term “toxicant-induced loss of tolerance” more fully describes the two-step process under scrutiny.

Keywords: Chemical sensitivity; Theory for disease; Environmental exposure; Environmental etiology; Toxicant-induced loss of tolerance

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1. Introduction

The Eskimos have many words in their language for “snow” — there is freshly fallen snow, snow with an icy crust on it that crunches underfoot, fine snow, snow that drifts, snow that clings, soft, deep snow, and so on (Woodbury, 1991).

Snow is an integral part of Eskimo life. In the United States, there are now more than a dozen names for chemical sensitivity: some of these names imply a particular cause (e.g. the petrochemical problem, chemophobia), some describe the effect (e.g. universal allergy, multiple chemical sensitivity), and others insinuate a particular mechanism (e.g. immune dysregulation, odor conditioning) (Ashford and Miller, 1991). "Chemical sensitivity" and "multiple chemical sensitivity" ("MCS") appear favored at present. These terms describe the most distinctive feature of the illness without presuming a particular etiology or mechanism. Notably, some feel that even "MCS" is too much of a legitimizing label and have suggested that "multiple symptom complex" might be less objectionable (Gots et al., 1993).

Some physicians and researchers believe that MCS is a psychogenic phenomenon which most closely resembles depression, somatoform disorder or post-traumatic stress disorder. Others think that MCS is caused by chemical exposures and, further, that chemical sensitivity may underlie a host of "recognized" chronic illnesses, including asthma, migraine headaches, depression, fibromyalgia, and chronic fatigue syndrome. Still others remain agnostic, awaiting more evidence before proffering opinions.

Authors of scientific articles have used the term "chemical sensitivity" in different ways and in different contexts to "mean just what they choose it to mean" (Humpty Dumpty, Lewis Carroll). Words have consequences and a shared understanding of the term "chemical sensitivity" is essential if Jabberwockian *nonscience* (read: nonsense) is to be avoided. The purpose of this paper is to explore the meanings that have been imputed to the term "chemical sensitivity," and, by the close of this paper, convince the reader of the seriousness of the current confusion over its meaning, and how more precise terminology could lead to clearer thinking and greater understanding in this area. Risk assessment, the focus of this conference, requires that we "count the bodies" of those who are afflicted. How we define chemical sensitivity greatly affects this count.

The history and phenomenology of chemical sensitivity, as well as the panoply of hypotheses

that have been advanced to explain it are discussed in detail elsewhere. In the past eight years, two reports sponsored by state agencies (Ashford and Miller, 1989; Bascom, 1989), two books written for occupational health professionals and researchers (Cullen, 1987; Ashford and Miller, 1991), and the proceedings of three federally-sponsored meetings that focused on chemical sensitivity (Association of Occupational and Environmental Clinics, 1992; National Research Council, 1992; Agency for Toxic Substances and Disease Registry, 1994) have been published. A review of these and other recent publications on MCS reveals that the term "chemical sensitivity" is most often used in one of three contexts: (1) to describe a symptom; (2) to serve as a kind of shorthand for an allegedly new medical phenomenon or syndrome; and (3) to characterize what some view as an emerging mechanism for disease. Depending upon which of these contexts is meant, the number and types of persons who might be chemically sensitive varies greatly, and there are enormously different consequences for patients, industry, policymakers and risk assessors. In the next sections, we will explore each of these contexts and the consequences which flow from them.

2. Chemical sensitivity: the symptom

The simplest and perhaps least judgmental application of the term "chemical sensitivity" has been its use to describe the symptom of feeling ill from chemical odors. While the word "cacosmia" has been used in the occupational health literature to describe this symptom, neither this term nor the word "dysosmia" fully convey the observation that MCS patients *feel ill* when they confront certain odors. An alternate term that would convey this might be "pathosmia." Illness from odors has been reported in 60% of a group of solvent-exposed workers (Ryan et al., 1988; Morrow et al., 1990). It also has been reported among agricultural workers following acute organophosphate intoxication (Tabershaw and Cooper, 1966) and among workers in chemical warfare agent production facilities (SIPRI, 1975).

Table 1
Frequency of chemical/odor sensitivity in selected populations

Population	n	Question posed	% Answering affirmatively
EPA office workers (EPA, 1989)	3955	Do you consider yourself especially sensitive to ... (various indoor air contaminants)?	31%
Arizona ^a elderly living in planned retirement community (Bell et al., 1994)	192	Do you consider yourself especially sensitive to certain chemicals?	34%
University of Arizona ^a college students in introductory psychology class (Bell et al., 1995)	809	Do you consider yourself especially sensitive to certain chemicals	28%
Rural North Carolinians (Meggs et al., 1994)	1027	Some people get sick after smelling chemical odors like those of perfume, pesticides, fresh paint, cigarette smoke, new carpet, or car exhaust. Other people don't get sick after smelling odors like these. Do any chemical odors make you sick?	33% (39% of women; 24% of men)

^aA haven for pollen-allergy sufferers in the past, Arizona is thought to have the highest percentage of atopic individuals of any state.

How prevalent is the *symptom* of chemical sensitivity, or pathosmia? To date, no randomized, population-based survey that would answer this question for the nation as a whole has been conducted. However, several smaller surveys suggest that 28–34% or approximately one-third of the population considers itself especially sensitive to certain odors (Table 1). Notably, most of the participants in these surveys who reported that certain odors made them feel ill were neither sick nor disabled. Thus, while approximately one in three Americans reports that certain odors cause illness, the majority of these individuals differ substantially from MCS patients. Whether with sufficient exposure any, some, most, or all of these individuals might develop MCS remains to be determined. Nevertheless, it seems fair to say that the symptom of feeling ill from chemical odors is not identical to nor specific for MCS.

Thus chemical sensitivity—the symptom—lacks specificity for the condition under scrutiny. It may also lack sensitivity. That is, individuals who may be chemically sensitive may not be aware that they are chemically sensitive (for example, migraineurs, chronic fatigue sufferers). “Masking” (to be discussed in a later section) may interfere with this awareness. Thus, the

symptom of chemical sensitivity or pathosmia, while prevalent in the general population, is not very specific, and, indeed, also may be insensitive as an indicator of illness associated with low level chemical exposures. Notwithstanding, the term “pathosmia” has value for descriptive clinical and research purposes. Its adoption for describing the symptom of feeling ill from chemical odors may be preferable to the term “chemical sensitivity” which has acquired other meanings, as shall be discussed.

3. Chemical sensitivity: the syndrome

A “syndrome” is “a *group* of symptoms or signs typical of a disease” (Webster’s, 1986). Many have objected to labelling chemical sensitivity a syndrome because the patients report such diverse symptoms. Indeed, while individual patients report that their symptoms occur reproducibly following exposure to specific substances, unlike other recognized syndromes there is no archetypical constellation of symptoms that constitutes MCS. This fact has thwarted development of a case definition for the illness. While a precise MCS case definition would be desirable for research purposes, restricting thinking about

chemical sensitivity to any immutable set of symptoms or number of organ systems could prematurely constrict the field of view. For example, some proposed MCS case definitions exclude asthma or depression on the grounds that these are “diagnosable” conditions. Yet asthma or depression might themselves be the consequence of low level chemical exposure. In contrast, *exposure (or event) driven studies*, for example studies of office workers in a sick building or residents of a community exposed to a toxic spill, could yield a fuller understanding of the range and nature of illnesses that ensue (National Research Council, 1992). More specifically, it is conceivable that exposure to emissions from new carpeting in a poorly ventilated office building could cause or exacerbate a panoply of conditions, with the occupants’ personal (genetic, nutritional, etc.) vulnerabilities determining which specific symptoms manifest in any individual case. Indeed, some researchers have suggested that RADS (Reactive Airways Dysfunction Syndrome), an asthma-like condition that develops after an acute chemical exposure and leaves its sufferers sensitive to chemically-diverse inhalants, may be a pulmonary manifestation of MCS (Meggs and Cleveland, 1993). Still others hypothesize that certain cases of depression and somatoform disorder may be caused or exacerbated by chemical exposures and thus could share the same biochemical underpinnings as MCS (Rosenthal and Cameron, 1991; Bell, 1994). Then there are odor-triggered migraines and seizures. Might these be induced by the same mechanisms that underlie MCS? Limiting the search for chemical sensitivity to any predetermined set of symptoms or clinical criteria makes little sense when we are in such an early observational stage in this illness.

At least five case definitions for research on chemical sensitivity have been published (summarized in Miller, 1994), yet consensus on a single definition has not emerged, again largely because of the heterogeneity of symptoms patients report. Miller and Mitzel (1995) compared two groups of MCS patients — 37 who attributed onset of their illness to a well-defined exposure to a cholinesterase-inhibiting pesticide and 75 who

attributed onset of their condition to remodeling of a building. Despite differences in *individual* symptom patterns and different initial exposures, the two *groups* exhibited strikingly similar frequencies and ordering of symptoms. The authors interpreted these findings as suggesting a shared mechanism or final common pathway leading to the same disorder in both groups.

Some view the fact that no symptom-based case definition for MCS has achieved broad acceptance as evidence that the condition does not exist. On the other hand, this lack of consensus could be a serendipitous clue that chemical sensitivity is not a *single* syndrome, but a *collection* of syndromes that share the same general mechanism, much as cholera, influenza and Rocky Mountain Spotted Fever share the same general mechanism, in this case, infectious transmission.

4. Chemical sensitivity: a mechanism for disease?

The Civil War marked the last major armed conflict fought in the world without knowledge of microbes or infectious disease (Sartin, 1993). A few years later, Pasteur, Lister, Koch and others made their discoveries which led to the germ theory of disease. Two-thirds of the approximately 660 000 deaths among soldiers during the Civil War were caused by infections, most frequently wound infections and epidemics. Diagnoses were based on clinical signs. Fever cases were divided into three categories: remittent, intermittent, and relapsing. Cases assigned to those categories likely included typhus, typhoid, malaria, abscesses, tuberculosis, leptospirosis, borrelia, pneumonia, influenza, infectious diarrheas and others. Brucellosis, tularemia, leptospirosis and Q fever likely were present too, but put in other categories such as “miasmatic diseases, unclassified.” Civil War surgeons commonly attributed diseases to toxic miasma or “effluvia” from the wet swamplands of the South where many battles were fought or to inadequate ventilation in the tents (Sartin, 1993).

It is possible that we may be at the Civil War stage in our understanding of chemical sensitivity. Chemical sensitivity could be an emerging mechanism or theory of disease, one that en-

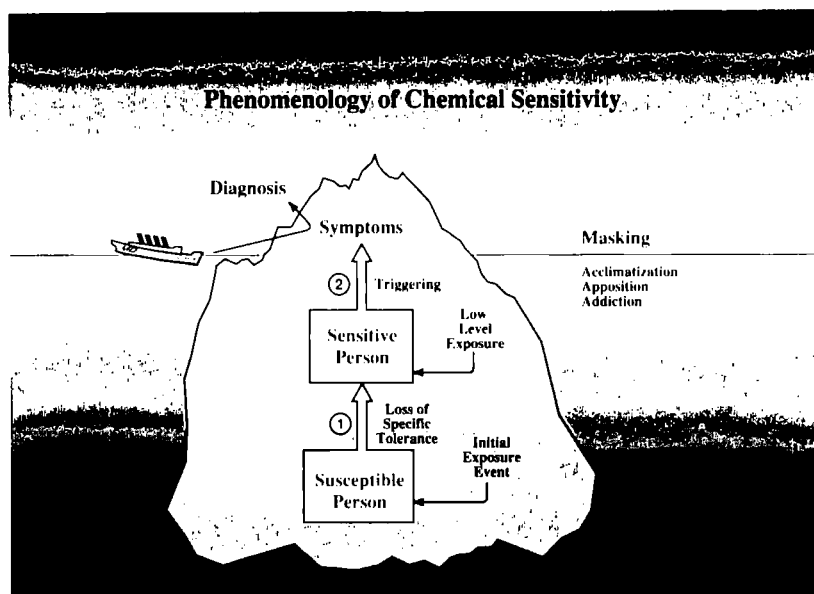


Fig. 1. Phenomenology of chemical sensitivity. Chemical sensitivity appears to develop in two stages: (1) loss of specific tolerance following acute or chronic exposure to various environmental agents, such as pesticides, solvents or contaminated air in a sick building, and (2) subsequent triggering of symptoms by extremely small quantities of previously tolerated chemicals, drugs, foods, and food/drug combinations (e.g. traffic exhaust, fragrances, caffeine, alcohol). Physicians formulate a diagnosis based upon symptoms reported to them by their patients. Because of masking, both physicians and patients may fail to "see" that everyday, low-level exposures may be triggering symptoms. Even when such triggers are recognized, an initial exposure event which may have initiated loss of specific tolerance may go unnoticed or may not be linked to the patient's illness.

compasses a wide range of chemical agents acting on different organ systems via different specific mechanisms, just as the category "infectious diseases" subsumes a wide range of vectors affecting different organ systems via different specific mechanisms resulting in heterogeneous symptoms. Is there any evidence to support such a notion?

If chemical sensitivity were a candidate for a theory of causation for disease, at the very least it would need to embrace MCS, the most prototypical of the chemical sensitivity "diseases," and would need to account for the clinical observations associated with MCS. These observations are discussed in detail elsewhere (Ashford and Miller, 1989, 1991; Miller, 1994) and summarized in Fig. 1. Briefly, chemical sensitivity appears to entail two steps: (1) induction, and (2) triggering. The inducing or initiating exposure may involve any of a wide variety of substances, including

pesticides, solvents, indoor air contaminants, drugs, etc. It may be acute as in a chemical spill, intermittent as in many industrial exposures, or chronic as in a sick building. *Loss of tolerance* appears to occur as a consequence of this initial exposure. Subsequently, extremely low levels of chemicals, levels that do not bother most people and were never a problem for that individual before, trigger symptoms. In addition, alcoholic beverages, caffeine, nicotine, various foods and drugs may trigger symptoms. On the surface, "loss of tolerance" may sound like a vague and ill-defined concept, the product of arm-chair theorizing. Clinically, it is neither vague nor ill-defined. What MCS patients describe is a loss of tolerance for *specific* inhalants, drugs, foods, etc. This loss of tolerance is reported to spread to an increasing number of substances as the problem progresses. When MCS patients are re-exposed to these specific substances, they say they experi-

ence a discrete constellation of symptoms. While the symptoms that are triggered by a given agent are highly individual, they are reportedly reproducible for a particular patient following a particular exposure, for example, headache with diesel exhaust, mental confusion with a certain fragrance, nausea with cashews, and so on. Notably, many MCS patients and Gulf veterans now forego chocolate, favorite foods like pizza, or alcoholic drinks because they say these make them so sick (Miller, 1994). Most of us would not give up these indulgences without good cause—there seems little secondary gain to be garnered from such abstinence, although some psychologists and psychiatrists, no doubt, would argue otherwise.

Thus, loss of specific tolerance is a focused, well-defined construct, one no more fuzzy than the General Adaptation Syndrome and its associated concepts of stress and stressors were when Hans Selye first introduced them.

Chemical sensitivity has been accused of contradicting the fundamental principles of toxicol-

ogy (Waddell, 1993). The same might have been said for allergy (or even cancer) when it was first discovered, and is even true now. Allergy's rules differ greatly from those of toxicology, and, if chemical sensitivity is real insofar as being a disease mechanism, it seems to follow still another set of rules. Chemical sensitivity appears to have major overlaps with toxicity, allergy and addiction (Table 2), yet it does not adhere to all of the rules for any one of these.

Like toxicity, chemical sensitivity appears to involve adverse responses to environmental chemical contaminants, yet, mechanistically, chemical sensitivity more closely approximates allergy in that both involve a two-step (induction, triggering) process and subsequent "hypersensitivity." As with addiction, patients with chemical sensitivity report stimulatory and withdrawal symptoms. Unlike addiction, these responses occur not only to drugs, but also apparently to combustion products, fragrances, solvents and even foods. However, instead of manifesting addicted behaviors (*L. ad* "toward" + *dicare* "pro-

Table 2
Features of chemical sensitivity that overlap addiction, allergy, and toxicity

Feature	Chemical sensitivity ^a	Addiction ^a	Allergy ^a	Toxicity ^a
Chemical/drug intolerances	+	+	+	+
Ambient air incitants	+		+	+
Food intolerances	+		+	
Alcohol intolerance	+	+		
Caffeine intolerance	+	+		
Withdrawal symptoms	+	+		
Craving, bingeing	+	+		
Sensitization	+		+	
Induction by chemicals	+		+	+
Induction by biologicals			+	
Multi-system symptoms	+	+	+	+
Frequent CNS symptomatology	+	+		+
Well-defined mechanism(s)			+	+
Genetic susceptibility	+	+	+	+
Dose/response relationship	+		+	+

^aCategories are not "pure" and may overlap in a given host, e.g. haptenation of a chemical toxin may initiate an immunologic response; brain and liver toxicity may accompany alcohol addiction.

^bDose-response does occur for allergens: with the first, sensitizing exposure for a susceptible individual, there is a dose-response relationship; with subsequent exposures, the sensitized person also responds in proportion to dose, but at a much lower dose level (Waddell, 1993). The same kind of dose-response relationship may pertain for chemical sensitivity, but has not been tested. However, individuals with MCS report increasingly severe symptoms the longer they remain in an exposure situation, an observation which hints at a dose-response interaction.

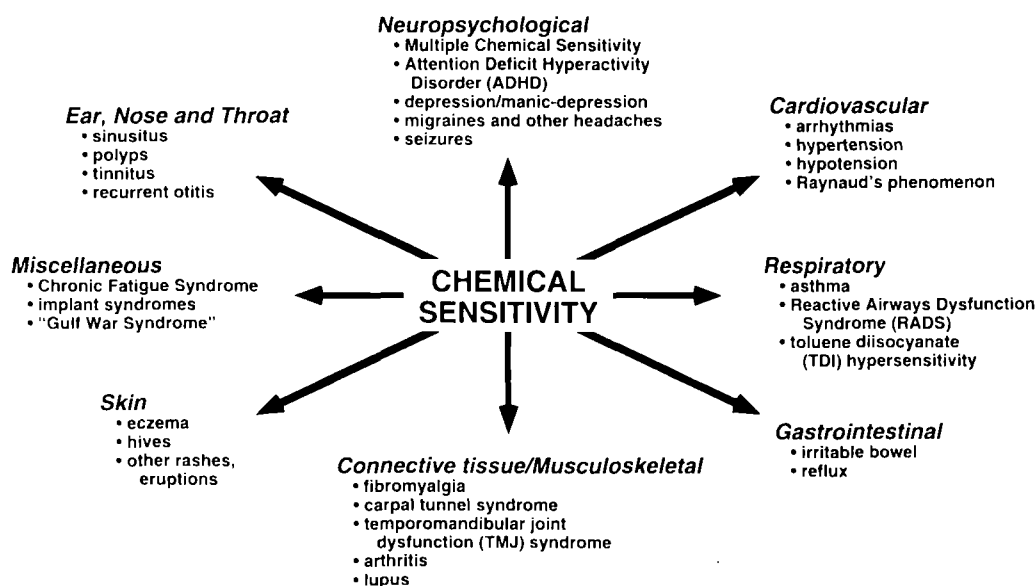


Fig. 2. Conditions that have been attributed to chemical sensitivity. (Of course, illnesses like depression, migraine, arthritis, hives, etc. may have many different etiologies. At most, chemical sensitivity might explain only a subset of these conditions. The question is, for each illness, how large is that subset and how might physicians distinguish those cases from similar cases with different etiologies).

claim”), patients act as though they are *ab*-dicted (L. *ab* “away from” + *dicare* “proclaim”) and assiduously *avoid* the very substances addicted individuals frequently favor, for example, alcohol, drugs, nicotine, and caffeine.

A major criticism of chemical sensitivity is that it has been claimed as a basis for “literally any physical or mental illness” (Waddell, 1993). Indeed, the range of illnesses that have been attributed to chemical sensitivity is enormous (Fig. 2) and involves any and all organ systems. Notably, and perhaps analogously, infectious diseases and immunological conditions also can affect virtually any organ system, so this criticism does not in any way negate the possibility that chemical sensitivity exists. In fact, close inspection reveals intriguing parallels between chemical sensitivity and the germ and immune theories of disease (Table 3). Each of these three theories embraces a wide range of specific agents or exposures. Included under each of these three categories are heterogeneous specific mechanisms (for example, the mechanisms of viruses vs. bac-

teria vs. rickettsia, or immediate vs. delayed-type hypersensitivity). Nonetheless, these diverse mechanisms still fall within the same general category, that is, infectious diseases or immunological diseases. Each of the three categories contains specific named syndromes or diseases. And each category contains processes that can affect literally any organ system. The specific manifestations of a given disease process in each of these categories depend on the nature of the original incitant and the vulnerabilities of the host, whether the category is infectious diseases, immunological diseases or chemical sensitivity. *Between* categories, symptoms are quite similar—malaise, rashes, headaches, shortness of breath, and diarrhea are common, non-specific manifestations for many illnesses. There is nothing pathognomonic about such symptoms. They can accompany an infectious process just as readily as an immunological or toxic one. It is the specific syndromes or named diseases within categories that have recognizable constellations of symptoms which facilitate diagnosis. Thus, rather

Table 3

Comparison of key features of three theories of disease: the germ theory, immune theory and chemical sensitivity theory

Disease theory	Explanation for disease	Symptoms	Particular diseases/syndromes	Agents	Exposure routes	Organ systems affected
Germ (Infectious)	Biological agent or "germ" multiplies in host (infection); germs can be transmitted to other organisms	Fatigue, malaise, fever, rash, headache, nausea, vomiting, diarrhea, shortness of breath, shock	Malaria, influenza, chicken pox, cholera, Lyme disease, AIDS, pneumonia	Bacteria, viruses, parasites, fungi, rickettsia	Inhalation, ingestion, injection, skin/mucous membrane contact	Any organ system or several at once
Immune	Host responds to foreign substance (antigen) by producing antibodies which "remember" the antigen and help ward it off in the future	Malaise, rash, pruritus, rhinorrhea, wheezing, shortness of breath, diarrhea, fever, laryngeal edema, shock	Allergic asthma, hives, poison ivy, penicillin allergy, peanut allergy	Pollen, mold, house dust mite, animal dander, foods, biologicals (drugs)	Inhalation, ingestion, injection, skin/mucous membrane contact	Any organ system or several at once
Chemical Sensitivity	Environmental exposure causes loss of specific tolerance in host, who subsequently develops symptoms when exposed to low levels of chemically diverse substances	Fatigue, malaise, memory difficulties, depression, irritability, headaches, digestive problems, shortness of breath, odor intolerance	Multiple chemical sensitivity, "Gulf War Syndrome" (?), chronic fatigue, syndrome (?), post-implant syndromes (?), reactive airways dysfunction syndrome (RADS)	Solvents, pesticides, combustion products, drugs, implants	Inhalation, ingestion, injection, skin/mucous membrane contact	Any organ system or several at once

than being a syndrome *per se*, chemical sensitivity has many of the earmarks of an emerging category of disease. Such an unproven, yet-to-be-tested general mechanism for a collection of illnesses is a *theory of disease*.

Recalling the critics view that chemical sensitivity is not a syndrome because no definable set of symptoms is associated with it, the critics make an important point: chemical sensitivity may no more be a syndrome than infectious diseases and immunological diseases are syndromes. Nor is there any conceivable case definition that would cover all infectious diseases or all immunological diseases. Case definitions simply have limited utility when we are discussing categories of disease.

Could chemical sensitivity be an emerging new theory of disease? In 1868, while commenting on the usefulness of the germ theory of disease, Max Boehr provided a remarkably insightful and concise synopsis of the criteria for choosing among alternative theories (Carter, 1985). He noted that "the theory of infection has the characteristic of all good pathological and physiological theories; it provides a unified, clear, and entirely intelligible meaning for a whole series of anatomical and clinical facts and for the relevant experiences and discoveries of reliable observers during epidemics." Likewise, chemical sensitivity is a theory of disease that could unite disparate clinical observations and that may enable practitioners to predict patient responses under conditions of

Table 4
Frequency of selected symptoms reported as severe^a by Gulf veterans, MCS patients and controls

Symptom	Gulf veterans (<i>n</i> = 59)	MCS pesticide-exposed (<i>n</i> = 37)	MCS remodeling-exposed (<i>n</i> = 75)	Controls ^b (<i>n</i> = 112)
Fatigue	78%	68%	52%	3%
Depression	29	49	33	6
Headaches	53	38	31	5
Shortness of breath	38	43	31	2
Asthma or wheezing	12	27	15	0

^aParticipants rated their symptoms on a 0–3 scale: 0, not at all a problem; 1, mild; 2, moderate; 3, severe. Frequencies listed in this table reflect ratings of severe (3) only.

^bAge, sex and education-matched to the two MCS groups (37 + 75 = 112).

exposure and avoidance. While clinical observations on MCS accumulated to date do not constitute proof of the condition's existence, they are hypothesis-generating and provide the foundation for what could be an emerging theory of disease, a theory worthy of careful scientific testing.

Some have proposed that the same mechanisms that are operative in chemical sensitivity might underlie conditions like fatigue, depression, headaches and asthma. If one compares the frequency of these particular conditions among groups of ill Gulf veterans and MCS patients to the frequency of these same conditions among controls (matched for age, sex and education to the MCS patients), 5 to 15 times as many Gulf veterans and MCS patients report *severe* fatigue, depression, headaches, shortness of breath, asthma or wheezing as controls (Table 4). Thus, Gulf veterans and MCS patients who attribute their illness to an "exposure event" represent an enriched sample of the population for these conditions. This finding suggests that at least a subset of persons suffering from headaches, chronic fatigue, asthma or depression might be chemically sensitive. It is noteworthy that persons with these conditions often share the same exposures and environments that MCS patients say caused their illness.

Anomalies often pave the way for discovery. The anomalous observation that individuals who survived a particular infection rarely contracted that infection again led to the immunologic con-

cept of disease. The anomaly of MCS could likewise expand our thinking about disease causation. Thomas Kuhn (1970) observed that theories are "generally preceded by a period of pronounced professional insecurity. As one might expect, that insecurity is generated by the persistent failure of the puzzles of normal science to come out as they should. Failure of existing rules is the prelude to a search for new ones." Perhaps, we are in what Kuhn characterizes as a pre-paradigm period, a time "regularly marked by frequent and deep debates over legitimate methods, problems, and standards of solution, though these serve rather to define schools than to produce agreement."

5. Masking

If individuals with migraines, chronic fatigue, asthma or depression were suffering from chemical sensitivity, why wouldn't more of them report specific chemical intolerances just like MCS patients do? In fact, many MCS patients say that when they first became ill, they had no idea chemical exposures had anything to do with their symptoms. They say it was not until they avoided (accidentally or intentionally) a sufficient number of their problem incitants simultaneously that they noticed feeling better. Then, when they re-encountered something to which they were sensitive, their symptoms recurred. Thus, MCS patients claim that only through the tandem process of avoidance and re-exposure were they able to

learn which exposures triggered their symptoms. Had they not systematically avoided a wide range of exposures first, or “unmasked” themselves, accidentally or intentionally, most say they would not have figured out what was making them sick. This lay term, “masking,” sounds deceptively simple. In fact, what patients mean by masking is technically quite complex. Understanding masking may be fundamental to understanding chemical sensitivity, its potential role in chronic illness and how such a theory of disease might be tested scientifically. When MCS patients talk about “unmasking,” they are describing a complex phenomenon that is poorly understood but experientially recognizable to most of us. There are at least three components involved in masking: acclimatization, apposition and addiction (Fig. 3). “Unmasking,” that is, avoiding multiple potential incitants simultaneously, overcomes each of these three components of masking.

The most rigorous approach to unmasking, an approach developed in the 1950s by allergist Theron Randolph, involves placing an individual in an environmentally-controlled hospital unit (not an exposure chamber) and restricting food and drug intake for several days to a week. This approach (described in Ashford and Miller, 1991), eliminates any *acclimatization* that may have developed in a sensitive individual as a consequence of chronic or repeated exposure to an incitant, for example, indoor air contaminants in a sick building. It simultaneously allows the avoidance of inhalation, ingestion and dermal contact for most chemicals, foods, and drugs, thus preventing overlapping symptoms that might occur in a sensitive individual experiencing multiple, overlapping exposures (*apposition*). Finally, this approach interrupts any *addiction* due to repeated exposure to caffeine, alcohol, nicotine or other addictive substances. Fig. 3 depicts each of the components of masking. In effect, masking and unmasking pertain to the *state* of the patient—the underlying illness remains constant. Depending on background environmental conditions, chemical sensitivity seems to occur in masked and unmasked varieties which outwardly appear different but are intrinsically the same.

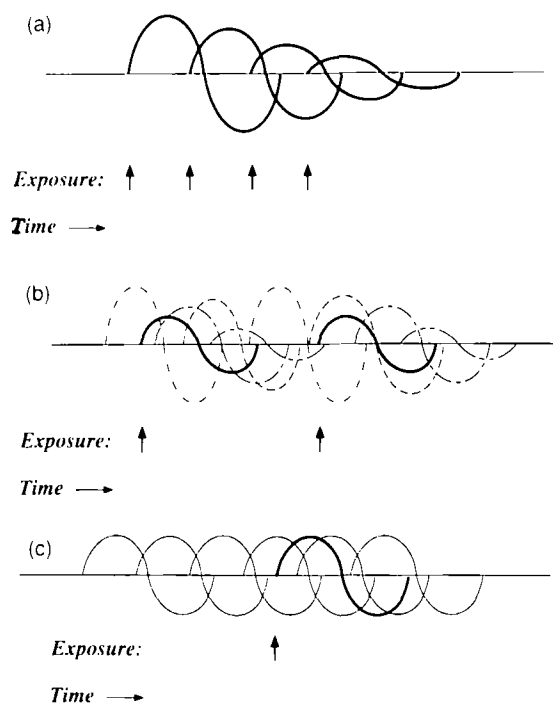


Fig. 3. Components of masking. Each biphasic curve is a graphical representation of symptoms occurring in a sensitive individual with onset and offset of a particular exposure. For solvents, caffeine, alcohol, nicotine, etc., the portion above the line represents stimulatory symptoms and the portion below withdrawal symptoms. Amplitude is proportional to symptom severity. For a person who is not particularly sensitive to the substance, the curves would be flat or nearly flat. Solid curves represent the effect of interest, that is, a response to a particular chemical or food one is trying to observe during a challenge with that substance. (A) Acclimatization: symptom severity decreases with repeated, closely-timed exposures to the same substance. Although seemingly paradoxical, sensitivity may increase during acclimatization. In real life, time intervals between exposure may vary greatly, so that a person may be acclimatized to varying degrees at different times, and thus, from day to day, experience varying intensity of symptoms. However, the most robust effect of a challenge would be expected in the sensitive individual who is not acclimatized. (B) Apposition: if an individual is sensitive to many different substances, then the effects of everyday exposures to chemicals, foods or drugs may overlap in time. This apposition of effects might yield an individual who feels bad most of the time, but the effect of any single exposure is not apparent either to the individual or his physician. Apposition would tend to mask the effect of interest in much the same way that background noise masks a sound of interest. (C) Addiction: a sensitive person who is addicted to caffeine, alcohol, nicotine, or other substances may deliberately take the substance at frequent, carefully-spaced intervals to avoid unpleasant withdrawal symptoms. Such exposures may also mask an effect of interest.

There are no scientific equivalents for the terms “masking” or “unmasking.” “Adaptation” and “de-adaptation” (terms previously used by this author) have other connotations that seem to confuse rather than clarify understanding of this concept; inevitably their use leads to a discussion as to whether adaptation or pseudoadaptation is occurring (for example, in cigarette smokers who develop apparent tolerance for the irritative properties of tobacco smoke, but may experience long-term deleterious consequences from tobacco use). Understanding masking may be crucial to understanding chemical sensitivity. As long as patients with depression, migraines, fatigue, etc. are masked, it may be impossible to tell whether there is any relationship between their symptoms and low level environmental exposures. They must first be unmasked. Testing such patients in a masked state would be like trying to find out whether headaches in a coffee drinker with a 10–15 cup per day habit were due to caffeine by giving him a cup of coffee and asking how it made him feel. It is intuitively obvious that the individual would need to stop using all or most caffeine (unmask him for caffeine) before a meaningful test of caffeine sensitivity could be performed. Falsely negative challenges are likely to result from failure to unmask. This experimental requirement of unmasking brings to mind the enormous difficulty researchers encountered during the late nineteenth century in trying to isolate the organism responsible for tuberculosis. Many researchers collected fluids from TB patients but were unsuccessful in culturing any organism. At the time, these researchers were unaware that the organism was extremely fastidious and would only grow out after weeks on a specialized culture medium. Some who failed to grow the organism concluded that TB was not an infectious disease at all. Correspondingly, our ability to “see” chemical sensitivities may rest upon optimizing experimental conditions, i.e. using the appropriate culture medium, in this case an environmental unit for unmasking and studying this phenomenon. Absent such an approach, erroneous conclusions about the existence of MCS may be reached as a consequence of inadequately

designed experiments resulting in falsely negative data.

6. Testing the theory of chemical sensitivity: the need for postulates

Following the introduction of the germ theory of disease in the late 1800s, many overly enthusiastic researchers employing careless bacteriological technique claimed to have discovered the causative agents for diseases such as TB or Yellow Fever. So frequent were these pronouncements and subsequent retractions that in 1884 the President of the New York Academy of Medicine, Abraham Jacobi, “lamented the ‘bacteriomania’ that had swept the medical profession” (Warner, 1985). In order to preclude further such pseudodiscoveries, Koch, who identified the organisms that cause tuberculosis, anthrax and cholera, suggested adoption of a set of rules for etiological verification, now known as Koch’s postulates:

- (1) The microbe must be present in every case of the disease.
- (2) It must be isolatable in pure culture.
- (3) Inoculating a healthy animal with the culture must reproduce the disease.
- (4) The microbe must be able to be recovered from the inoculated animal and grown again.

In comparable fashion, research on chemical sensitivity today is in need of a set of scientific principles or postulates that will ensure that causal determinations in this area are scientifically based. Fig. 4 illustrates use of an environmental medical unit as a means of testing responses to low level environmental exposures, and depicts four postulates which, if met, would establish proof of a cause-and-effect relationship between symptoms and a particular exposure or incitant, if such a relationship exists. These postulates are:

- (1) When the sensitive individual simultaneously avoids all chemical, food, and drug incitants, remission of symptoms occurs.
- (2) Symptoms occur with reintroduction of an incitant.
- (3) Symptoms resolve when the incitant is again avoided.

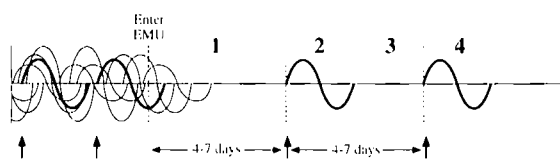


Fig. 4. Graphical representation of chemical sensitivity postulates. In the left-most portion of the figure, before entering an environmental medical unit (EMU), a chemically sensitive individual is experiencing symptoms in response to multiple exposures (chemicals, foods, drugs). Effects overlap in time. The effect of any particular exposure does not stand out from those of other exposures and the person's symptoms appear to wax and wane unpredictably over time. Postulate 1: when all chemical, food and drug incitants are concurrently avoided, remission of symptoms occurs. Postulate 2: symptoms occur with reintroduction of an incitant. Postulate 3: symptoms resolve when the incitant is again avoided. Postulate 4: re-exposure to the same incitant, within an appropriate window of time (estimated to be about 4–7 days), produces the same symptoms. For research purposes, challenges should be conducted in a double-blind, placebo-controlled manner.

(4) With re-exposure to the same incitant, the same symptoms recur, provided that the challenge is conducted within an appropriate window of time (ideally 4–7 days after the last exposure to the incitant).

Note that for research purposes, challenges of this type should be performed in a double-blind, placebo-controlled manner (Ashford and Miller, 1991). This approach could be extended to patients with MCS, chronic fatigue, migraines, seizures, depression, asthma, and other conditions to determine whether or not a particular person's illness is a *forme masquée* of chemical sensitivity.

What evidence is there that unmasking patients in an environmental unit and adhering to a 4–7 day window of time between challenges are important for this process? Only the observations of thousands of credible patients and dozens of physicians who have attempted this maneuver. Physicians and patients who have followed this procedure report impressively robust symptoms following food and chemical challenges. Given that clinical observations are the wellspring of most new medical ideas, we must guard against dismissing these patients' reports without trying

first to recreate the circumstances in which they say their responses are most clearly elicited. Some researchers may argue that an environmental unit and unmasking should not be necessary if patients are experiencing symptoms with daily exposure. It is true that an effect may be seen with exposure challenges outside of a unit. However, certain problems can be anticipated. First, patients' responses will not be as robust if unmasking and appropriate timing between challenges are not considered. But, more concerning, patients' responses may not be reproducible from one day to the next. For example, if patients must drive through heavy traffic to get to an exposure chamber in order to undergo a challenge, their responses to the challenge may be blunted or perhaps disappear entirely. Conversely, if a placebo is administered, sensitive individuals might still be experiencing delayed effects of their exposure to car exhaust while in transit to the laboratory, and falsely positive responses could occur.

7. Chemical sensitivity: the need for new terminology

Applying the moniker "chemical sensitivity" to the theory of disease described above fails to convey adequately either the potentially disabling nature of the condition or its induction by an earlier exposure event. The two-step process that has been described for chemical sensitivity begins with a chemical exposure which appears to be "toxic," that is, it causes adverse effects in at least a subset of individuals (i.e., when they subsequently are exposed to different substances). These individuals report life- and career-disrupting disability following an identifiable initial exposure. While Paracelsus aptly stated that dose makes the poison, in truth, "dose + host" makes the poison (for example, pack-years of tobacco smoked + the α -1-antitrypsin-deficient individual). Admittedly, the nature of the initial "toxicity" in chemical sensitivity departs radically from that of classical toxicity (Table 2). Clinically, this "toxicity" more closely resembles allergic sensitization, although, here again, there are major differences, which include the exquisite specificity of

antibodies for antigens versus the spreading of sensitivities to structurally unrelated chemicals that is reported by chemically sensitive patients.

In effect, chemical sensitivity is a sort of “cryptotoxicity.” “*Crypto*” (Gk. “hidden”) because of:

(1) The frequently hidden or imperceptible nature of the initial exposure(s) that causes loss of specific tolerance. This event may go unnoticed entirely or may not be connected causally with onset of illness by patient or physician. For example, an illness that develops following routine household extermination or administration of a general anesthetic may be attributed to some other cause. If several residents of a home recently treated with pesticides develop flu-like symptoms at the same time, an infectious cause may be assumed erroneously.

(2) The diversity of clinical presentations that occur, even among those who share the same inducing exposure event(s) (e.g. identically or near-identically exposed family members or co-workers). Such symptom heterogeneity in an exposed group would tend to “hide” the presence of a discrete illness, thus thwarting standard epidemiological approaches to investigating an outbreak.

(3) Masking via acclimatization, apposition and addiction, which have been described previously. Following loss of specific tolerance, masking obfuscates the relationship between symptoms and triggering exposures.

The term “toxicant-induced loss of tolerance” (acronym “TILT”) might describe this cryptotoxic theory of disease more parsimoniously. An analogy comes to mind here: with a pinball machine, a player has just so much latitude—he can jiggle the machine, nudge it, bump it, rock it, but when he exceeds the limit for that machine, the “TILT” message appears, the lights go out, and the ball cascades to the bottom. The machine’s tolerance has been exceeded and no amount of effort will make the bumpers or flippers operate as they did before. The game is over. A colleague recently suggested that another reason a pinball analogy was apt was the fact so many MCS patients bounce around from one specialist to another. Indeed the average MCS

patient in one study had consulted nearly ten physicians (Miller and Mitzel, 1995).

Is *another* name for chemical sensitivity really necessary? Notably, the term “allergy” might have sufficed. Patients with chemical sensitivities spontaneously refer to their responses as “allergies.” Indeed, when Von Pirquet coined the word “allergy” in 1906, he defined it as “altered reactivity” of *whatever* origin. The term originally embraced both immunity and hypersensitivity. In 1925, European allergists influenced their American counterparts to redefine allergy in the context of antibodies and antigens. A few American allergists objected, observing that hypersensitivity in some patients could be occurring on a non-immunologic basis. In 1967, the discovery of IgE cemented the antibody-antigen definition of allergy into place, apparently permanently. Allergists have spent many hours instructing the MCS patients who consult them that what they have is not an allergy.

8. Association versus causation

Critics of MCS correctly observe that “humans have a desire to assign a cause for everything.” The history of mankind is filled with examples of man’s attempts to assign cause to every event, particularly to illness, misfortune, or death (Waddell, 1993). The question is, how do we distinguish between a chance association and true cause and effect? Sir Austin Bradford Hill (1965) offered nine criteria that have been widely used by epidemiologists to help make this distinction: (1) Strength of the association, i.e. between the exposure and the illness. For example, Percival Pott observed an enormous, perhaps 200-fold increase in scrotal cancer among chimney sweeps versus workers not exposed to tar or mineral oils, a strong association indeed. However, Hill cautions, we should not be too ready to dismiss a cause-and-effect hypothesis merely on the grounds that the observed association appears slight, because there are many instances in medicine when this occurs, yet a cause-and-effect relationship exists. For example, only a few persons who harbor meningococcus develop meningitis

from it, and only a few individuals who are stung by bees develop anaphylaxis. Analogously, only a few persons exposed to certain pesticides or a sick building appear to develop MCS.

(2) Consistency. Have different people in different places and times observed the association? Hill considers this especially important for rare hazards or conditions. With regard to chemical sensitivity, multiple observers have independently described chemical sensitivity arising in persons exposed to organophosphate pesticides (Rosenthal and Cameron, 1991; Cone and Sult, 1992; Miller and Mitzel, 1995).

(3) Specificity of the association. The more the association is limited to specific exposures and/or to specific types of disease, the clearer the case for causation. Research on inducing exposures for MCS might reveal strong, specific associations. With respect to triggering, there appears to be lack of specificity both in terms of exposures and symptoms. However *individual* MCS patients report specific symptoms with specific exposures. Unlike for cancer or heart disease, cause and effect for symptom triggering in MCS can be tested experimentally in humans, providing direct experimental measurement of the specificity of the association (if it exists), the strongest form of evidence possible for an environmentally-related illness.

(4) Temporality. Does the exposure precede the illness? Some authors have noted depression or somatoform tendencies in some MCS patients that preceded their "initiating" exposure event. Perhaps the strongest evidence for temporality is the temporal cohesiveness between exposure and onset of symptoms that has been observed in large exposure groups, for example, the Environmental Protection Agency's sick building occupants or the Gulf veterans, many of whom report new-onset intolerances and have no evidence of psychiatric problems predating their exposure.

(5) Biological gradient. An association that follows a biological gradient or dose-response curve strongly suggests causality. Hill acknowledges that it is frequently difficult to obtain a satisfactory measure of exposure. However, a dose-response relationship that has been inferred for allergic conditions (Waddell, 1993) may also per-

tain to chemical sensitivity: there is a dose-response relationship for the first, sensitizing exposure in a susceptible individual; with subsequent exposures, the now sensitized person also responds in proportion to the dose, but at a much lower dose level. In addition, MCS patients frequently report that the longer they remain in an exposure situation, the more severe their symptoms become and the longer they persist. Again, in contrast with cancer or other environmentally-related diseases, the triggering phase of chemical sensitivity lends itself to direct human testing of a dose-response relationship, thus obviating the need for speculation about a biological gradient.

(6) Plausibility. Hill comments that it is helpful if the causation we suspect is biologically plausible, but that *what is plausible depends upon the biological knowledge of the time*: "in short, the association we observe may be new to science or medicine and we must not dismiss it too light-heartedly as just too odd." In fact there are some medical conditions which have features that are strikingly similar to MCS and which are well-accepted, for example, Reactive Airways Dysfunction Syndrome (discussed previously) and Multiple Drug Allergy Syndrome (Sullivan, 1991). These parallel clinical observations may be signs pointing in the direction of biological plausibility for MCS.

(7) Coherence. The cause-and-effect relationship under scrutiny should not conflict with other generally known facts about the disease, e.g. the pathology or biochemistry of the illness. Since so little research has been done on MCS, so far this has not been a problem.

(8) Experiment. Experimental evidence can provide the strongest support for a cause-and-effect relationship. Perhaps one of the reasons MCS patients are so dogged in their insistence that chemicals are causing their symptoms is the strength of the experimental evidence they perceive when they deliberately avoid and then are re-exposed to incitants. Part of the appeal of MCS, at least to some environmental scientists, is that it poses an experimentally testable hypothesis, in contrast with most other environmentally-related illnesses of major concern. But, again, experimental conditions must be optimized, i.e.

unmasking in an environmentally-controlled hospital unit, if the most robust effect is to be seen. Currently, the *only* obstacle to these studies being undertaken is lack of funding.

(9) Analogy. Under certain circumstances, cause-and-effect can be inferred by analogy. The sensitivities reported by MCS patients are reminiscent of the heightened sensitivity to tobacco smoke reported by those who have recently quit smoking. Likewise, there are close parallels between MCS and addiction, in which food cravings and bingeing are also reported. MCS patients describe “going through withdrawal” or “detox” during which the symptoms they report are reminiscent of those reported by drug abusers, yet most MCS patients systematically avoid even mildly addictive substances. Other possible analogues to MCS are Reactive Airways Dysfunction Syndrome (RADS) and toluene diisocyanate (TDI) sensitivity, particularly the former in which a single major exposure may lead to hyperresponsiveness to multiple, chemically-unrelated inhalants. We must ask ourselves, if the airways can develop sensitivity to multiple chemicals, by analogy why couldn’t the central nervous system do so as well?

To Hill’s criteria, I might add a tenth criterion, one that would apply to symptoms (or illnesses) that are primarily subjective in nature:

(10) Unique symptomatology. The more obscure or unique a symptom is, particularly if it is reported by several independent exposure groups (for example, industrial workers, white collar professionals, Gulf veterans), the greater the likelihood of causation. For MCS, it would be difficult to imagine that the curious symptom of odor intolerance, which has been reported by demographically diverse groups following various exposure events, could be “invented” by all of them. Equally unexpected and counter-intuitive are MCS patients’ practices of avoiding fragrances, foods, alcoholic beverages, etc., that they formerly relished. Why would anyone who really liked pizza, chocolate or beer give them up unless they made them ill? Why would a mechanic who loved his job and used to think that WD-40 would make a wonderful perfume, suddenly report that odors at work made him ill, if in fact they did

not? Why would doctors, lawyers, teachers and others say they quit their professions because of severe mental confusion around fragrances and engine exhaust, if this weren’t the case? Scientifically, it would be absurd to dismiss such eccentric behaviors in otherwise sane individuals without searching exhaustively for a plausible biological basis.

Hill suggests that his criteria be used to “study association before we cry causation.” He further cautions that none of the criteria indisputably revokes a cause-and-effect hypothesis, and none is a *sine qua non*. In aggregate, these criteria assist in determining causation. As discussed previously, chemical sensitivity appears to involve two steps: Induction by a major or repeated exposure, and (2) subsequent triggering of symptoms by chemically-unrelated, low level exposures. Verification of the second of these two steps lends itself to direct experimental testing. Validation of the first step may rest upon epidemiological investigations and animal studies.

9. Conclusion

If we now begin to speak of chemical sensitivity—the theory of disease, instead of chemical sensitivity—the symptom or the syndrome, the types and number of individuals potentially affected by the condition shift dramatically. While roughly one-third of the population reports the *symptom* of chemical sensitivity, only a fraction of these individuals suffers from a *syndrome* that disrupts their health or lifestyle. In contrast, chemical sensitivity—the *theory of disease* posits that familiar, chronic conditions like depression, migraine, fatigue, and asthma can arise from environmental exposure. The health care costs associated with these conditions are undeniably enormous. Notably, many of these same conditions also appear to be becoming more prevalent, which should further pique our curiosity about environmental causation, particularly given the exponential increases in synthetic organic chemical and pesticide production that have taken place in this country since World War II, coupled

with the fact that most Americans spend 90% or more of their day indoors, often in tightly constructed buildings with poor air quality.

How we define and conceptualize chemical sensitivity drastically affects our perspective regarding the seriousness of “low level” environmental exposures. As a symptom, chemical sensitivity or pathosmia generally is not disabling; as a syndrome, multiple chemical sensitivity is uncommon (although if only 1% of Americans were affected, it would still amount to a few million people). Those who see chemical sensitivity as an emerging theory for disease see something profoundly different and deeply concerning.

Only carefully designed studies in a controlled environment will answer the complex questions before us concerning the environmental etiologies of many chronic diseases. Studies of this kind will be essential for determining what role toxicant-induced loss of tolerance plays, if any, in human disease. From the standpoint of public health, if it were to be determined that chemical sensitivity was limited to a small group of vulnerable individuals in the population, perhaps strategies for protecting or accommodating them could be devised, such as special ventilation, working at home, wearing respirators, etc. Indeed such things already are being done. On the other hand, if chemical sensitivity is an emerging theory of disease that applies not only to MCS, but also to depression, migraine, asthma, chronic fatigue syndrome, illnesses associated with implants, and other conditions, the stakes go up considerably. Medical care costs in this nation have risen from 5.3% of gross domestic product in 1960 to 13.9% in 1993, with a dollar value exceeding \$1 trillion, nearly \$4000 per person (Grumbach and Bodenheimer, 1994; Levit et al., 1994). An important question is, how much does toxicant-induced loss of tolerance contribute to this sum?

These are vexing questions that go against the grain of accepted explanations concerning the origins of illness. In recent times, many chronic diseases, addiction, and violence have been explained in whole or in part in terms of the psyche and stress. An enormous amount of research has been devoted to these explanations. There are

about 37 000 psychiatrists and 241 000 psychologists in the United States (Roback et al., 1994; Statistical Abstract of the United States, 1994). Any theory of disease so bold as to suggest that depression, anxiety, panic attacks or fatigue might be caused by chemical exposures should expect a less than enthusiastic reception. Yet, most would agree *in principle* that organic bases for illnesses should be ruled out before psychological explanations are invoked. In medicine, millions of dollars are devoted to the study of the chronic conditions discussed here and to identifying psychological therapies and drug interventions. Yet, *what if* such therapies alleviated some but not all symptoms, and in the meantime causative exposures were overlooked? Such a notion seems farfetched, yet it is precisely what some heretical scientists and physicians now propose. A skeptical regard for such speculation by most practitioners should be viewed as a rational response to the flurry of pronouncements and papers of varying reliability that have appeared on chemical sensitivity in recent years. Wherever the truth lies, the costs of not pursuing scientific resolution of these questions are potentially enormous.

Perspective is important. Finding a biological marker for chemical sensitivity may prove as difficult as finding the bacterium that was causing cholera or identifying IgE in allergic diseases. Generally speaking, treatment and intervention need not await the discovery of a marker. Hand washing, sanitation, and allergy shots were all introduced based on clinical observations. Physicians over the centuries have had to tolerate uncertainty and cautiously adopt new therapies while awaiting scientific explanations, but never before in a nation or time with such high-tech medical prowess and vested corporate interests, neither of which has much enthusiasm nor patience for chemical sensitivity.

Science is not about belief. Science is about “guess and test.” A new “guess,” perhaps an emerging theory of disease that parallels the germ theory, has come to our attention. The theory suggests that certain costly, chronic illnesses may be caused by familiar exposures. The theory insinuates that environmental exposures may

cause loss of tolerance for specific chemicals, foods and drugs, that is, toxicant-induced loss of tolerance. The question is, shall we expend scant resources to explore this theory, or will we continue the present debate?

"When I use a word," Humpty Dumpty said, in rather a scornful tone, "it means just what I choose it to mean—neither more nor less."

"The question is," said Alice, "whether you can make words mean so many different things."

"The question is," said Humpty Dumpty, "which is to be master — that's all."

Lewis Carroll (emphasis added)

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Letters to the Editor

Readers are invited to submit letters for publication in this department. Submit them to: The Editor, Journal of Occupational and Environmental Medicine, PO Box 370, Bryn Mawr, PA 19010. Letters should be typewritten and double spaced and should be designated "For Publication."

Multiple Chemical Sensitivity Syndrome

To the Editor: In reference to "Multiple Chemical Sensitivity Syndrome: A Clinical Perspective" Parts I and II by Sparks et al (*J Occup Med.* 1994; 36: 718-737), I take exception to the statement that "Although general consensus was reached on an approach to clinical evaluation and management of MCS patients, the acknowledged contributors and reviewers do not agree on every point." While I was a contributor, I do not concur with the so-called "general consensus" presented in these articles. The first paper, which addresses competing hypotheses for MCS, contains a sufficient number of "mays" and "mights" that it could be described as "technically correct." However, ultimately, the caveats and tentative hypotheses are abandoned when the authors take sides by recommending primarily psychological interventions. To focus primarily on psychological interventions without adequately discussing environmental interventions, as these authors do, is identical to the recommendation that would follow from the conviction that the patients' problems were psychogenic in origin.

When I was invited to be a co-author on this paper, I declined because of its emphasis upon psychological interventions and minimal discussion of the potential role of chemicals and foods in the illness and upon trial-exposure reduction. Sparks aptly describes the "vacuum created by lack of data" on MCS. But when data are lacking, there is no basis upon which to recommend psychological therapies over environmental interventions except the authors' unsubstantiated belief that the patients' problems are psychogenic. Patients often are helped by psychological sup-

port no matter what the origin of their problems, but that support must not substitute for interventions that address possible physiological origins of their problems.

From a recent survey we conducted of 206 MCS patients with an average educational level of almost four years of college, the majority rated avoidance of problem chemicals (71%) and foods (54%) as "very helpful." Fifty-two percent of the 206 respondents had also tried psychological or psychiatric therapies, but only 17% of those who had tried them rated them as "very helpful." These patients, while recruited via announcements in patient newsletters, clearly feel that avoidance of problem chemicals and foods has been more helpful to them than psychological therapies. Where are the clear data upon which Sparks et al base their support for psychological interventions?

Finally, Sparks et al state that "the burden of proof rests with the proponents of avoidance that it is effective in reducing symptoms and is necessary to prevent toxic injury." Given the lack of funding for research on MCS, scientific proof one way or the other is likely to take years. In the meantime, how are patients to prove their need to avoid exposures for purposes of compensation, insurance coverage, or acceptance by the medical community? I can think of no other instance in medicine where we reject what the majority of patients (particularly such well-educated patients) tell us exacerbates and ameliorates their symptoms without first exploring their observations as potentially valuable clues.

While MCS is an understudied condition, data are emerging.^{1,2} As a practitioner, I would not wish to be caught in the uneasy position a few

years hence of not having advised patients to avoid exposures to substances that caused them permanent harm. Anecdotal reports of individuals with MCS who were diagnosed early, avoided further exposure, and recovered³, suggest that early intervention could prevent long-term disability for some individuals. Perhaps prevention of MCS is where we should be placing our emphasis—once the condition develops, *no* treatment appears satisfactory.

In sum, Sparks et al correctly diagnose the problem—lack of research on MCS—but their recommendations for clinical management are unjustified and simply reveal to the reader, and to the patients by the way, that in spite of their "mays" and "mights," they already have made up their minds. What to do until the data comes? Discuss with patients the possibility of MCS if symptoms and circumstances suggest it. Describe the divergence of opinion in the medical community in an open and honest manner. Discuss treatment options others have used, including psychological support and avoidance strategies, and the lack of peer-reviewed publications containing data as to their efficacy. Maintain agnosticism, while conveying an earnest desire to see patients improve. Schedule ample time for visits and regular visits so patients can discuss their problems and concerns adequately. As Sparks et al correctly observe, "The evaluation of a patient presenting with MCS may take several hours and it is necessary to allot sufficient time, even if inadequately reimbursed."

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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."

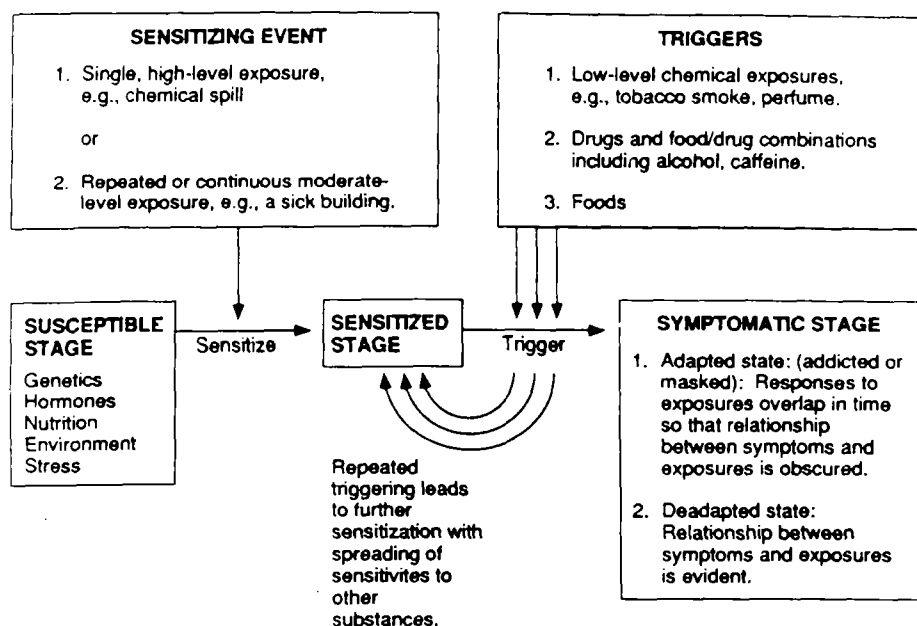


FIGURE 1. Phenomenology of Multiple Chemical Sensitivity.

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

¹Early 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.

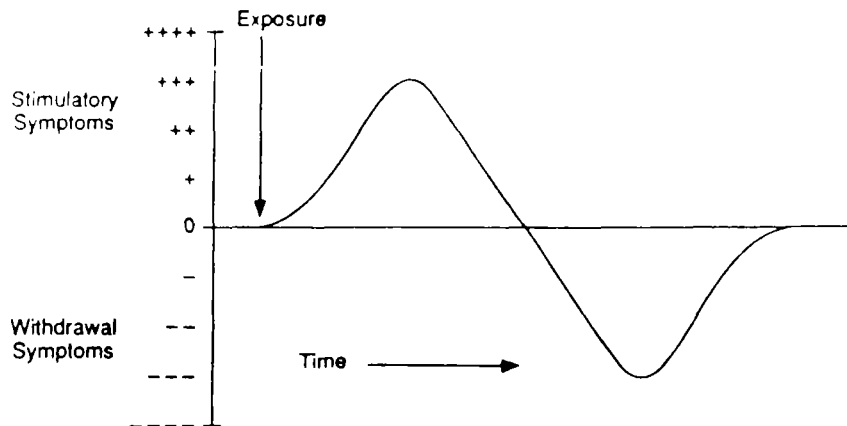


FIGURE 2. Graphical representation of symptom progression in a sensitive individual following exposure to a single substance (from O'Banion, *Ecological and Nutritional Treatment of Health Disorders*, 1981; courtesy of Charles C. Thomas, Publisher, Springfield, Illinois). The sine wave is a graphical 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.

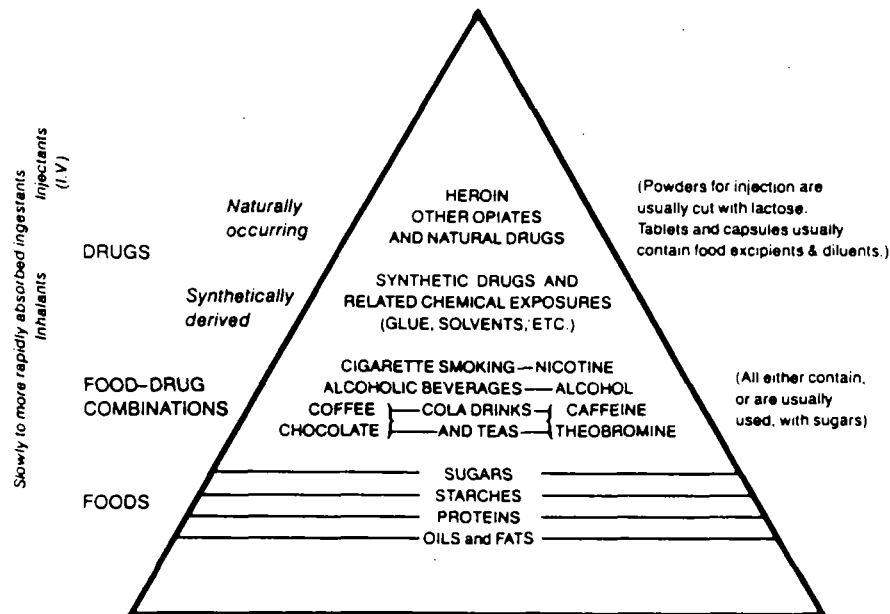


FIGURE 3. Addiction pyramid, after Randolph (1980).

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 (Cathelbras 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)

Symptom	Ranking		Mean symptom severity**	
	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).

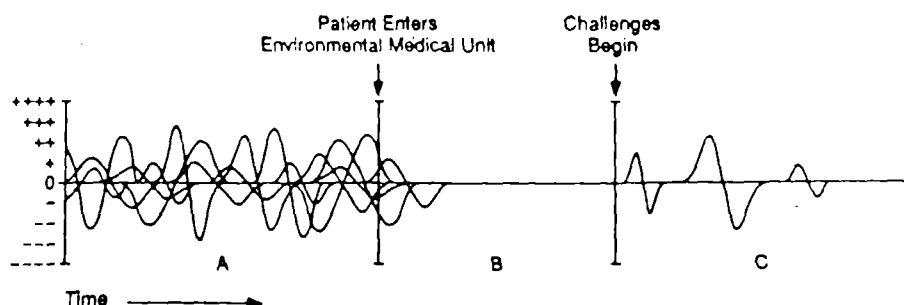


FIGURE 4. Hypothetical graphical representation of an individual's symptoms before and after entering an environmental unit (Ashford and Miller, 1991; © Van Nostrand Reinhold, 1991). In Time Period A, prior to entering an environmental medical unit (EMU), a chemically sensitive individual is responding 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	<u>Physiological</u> : Nasal airflow resistance, odor detection threshold, heart rate, BP, respiratory rate	<u>Physiological</u> : 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	<u>Immunological</u> : 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)	<u>Immunological</u> : Scattered tests out of normal lab ranges, but no significant or consistent abnormalities
Leznoff 1993	Self-reported MCS with Type A or B symptoms: <u>A</u> : Breathlessness & lightheadedness <u>B</u> : 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)	<u>Type A</u> (15 patients): Pulmonary function, pCO ₂ , pO ₂ . <u>Type B</u> (5 patients): Laryngoscopy, phonograms	<u>Type A</u> : 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 . <u>Type B</u> : 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 family referral	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 MCS¹

	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

¹Sources: 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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Chemical Sensitivity Attributed to Pesticide Exposure Versus Remodeling

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Department of Family Practice
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San Antonio, Texas

ABSTRACT. One hundred twelve individuals who reported onset of multiple chemical sensitivity following well-documented exposure to either (1) a cholinesterase-inhibiting organophosphate or carbamate pesticide or (2) remodeling of a building completed mail-out/mail-back questionnaires concerning their exposure, symptoms, sensitivity to ingestants and inhalants, utilization of health-care resources, and impact of their illness on lifestyle. It was hypothesized that if multiple chemical sensitivity resulted from neurotoxic exposure, then organophosphate-exposed respondents should report greater severity of illness resulting from the relatively greater neurotoxicity of this class of chemicals. Pesticide-exposed and remodeling-exposed multiple chemical sensitivity groups reported similar patterns of symptoms and identified similar inhalants and ingestants as triggers for their symptoms; these results suggested a common mechanism (biological and/or psychological) for their conditions. The pesticide-exposed group, however, reported significantly greater symptom severity than did the remodeling-exposed group, especially for neuromuscular, affective, airway, gastrointestinal, and cardiac symptoms. These findings provide evidence for (1) a possible biological basis for multiple chemical sensitivity and (2) a distinct pathophysiology or final common pathway for the condition that, while as yet undefined, appears to be shared by these two groups. Although subjective multisystem health complaints characterize both multiple chemical sensitivity and somatoform disorder, features of this multiple chemical sensitivity sample were inconsistent with somatoform disorder, i.e., onset after 30 y of age in 83%, the predominance of severe cognitive symptoms, and attributions of environmental causation. No group differences were found with respect to lifestyle impact. Eighty-one percent of respondents said they had been working full-time at the time they were exposed, yet at the time of the survey (on average, 7.7 y post exposure) only 12.5% were working full-time. The majority said they had quit their jobs, changed jobs, or changed careers because of their illness. Approximately 40% reported that they had consulted 10 or more medical practitioners. The persistent, disabling neuropsychological symptoms reported by these multiple chemical sensitivity groups are strikingly similar to those reported among individuals exposed occupationally to pesticides and solvents. These parallel findings suggest that the types and levels of exposures associated with extermination and remodeling may not be inconsequential, at least for a subset of the population. Further studies from a variety of perspectives, including human challenge studies and the development of animal models, are needed to define the pathophysiological and psychological mechanisms underlying this costly condition.

**CURRICULUM VITAE
CLAUDIA S. MILLER, M.D., M.S.**

Date of Preparation 10/1/96

I. GENERAL INFORMATION

A. Personal Data

1. Citizenship Status: USA
2. U.S. Social Security No.: 388-52-5166

B. Education

1981-1985	M.D.	Medicine	University of Texas Health Science Center, San Antonio, Texas
1968-1969	M.S.	Environmental Health	University of California School of Public Health, Berkeley, CA
1965-1968	B.A.	Molecular Biology	University of Wisconsin, Madison, Wisconsin

C. Post-Graduate Training

1988-1990	Fellowship	Allergy & Immunology	University of Texas Health Science Center, San Antonio, Texas
1986-1988	Residency	Internal Medicine	Brackenridge Hospital, Austin, Texas
1985-1986	Internship	Internal Medicine	Brackenridge Hospital, Austin, Texas

D. Academic Appointments

9/94-Present	Adjunct Assistant Professor of Environmental Sciences	University of Texas School of Public Health
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9/92-Present	Assistant Professor, Environmental and Occupational Medicine, Family Practice	University of Texas Health Science Center, San Antonio, Texas
7/91-8/92	Assistant Professor, Environmental and Occupational Medicine, Family Practice and Allergy & Immunology, Pediatrics	University of Texas Health Science Center, San Antonio, Texas
7/90-6/91	Clinical Assistant Professor, Allergy & Immunology, Pediatrics	University of Texas Health Science Center, San Antonio, Texas
7/88-6/90	Assistant Instructor, Allergy & Immunology, Pediatrics	University of Texas Health Science Center, San Antonio, Texas

E. Other Employment

1994-Present	Medical Staff Member	Audie Murphy VA Hospital, San Antonio, Texas
1991-Present	Medical Staff Member	University Hospital, San Antonio, Texas
1992-Present	Consultant to the Chief of Staff on Persian Gulf Veterans' Illnesses	Houston VA Medical Center
1977-1979	Occupational Health Consultant	Lake Forest, Illinois
1975-1977	Industrial Hygienist	United Steelworkers of America Pittsburgh, Pennsylvania
1973-1975	Industrial Hygienist and Industrial Hygiene Training Director	Occupational Safety and Health Administration National Training Institute, Chicago, Illinois

1971-1973

Industrial Hygienist

University of California Medical
Center, San Francisco, California

F. Certification and Licensure

1. Certification

American Board of Allergy/Immunology 1991 # 3378

American Board of Internal Medicine 1989 #123017

Federal Licensing Examination (FLEX) 1988
(components 1 and 2)

2. Recertification

n/a

3. Licensure

<u>State</u>	<u>Date Issued</u>	<u>Perm/Temp</u>	<u>Number</u>	<u>Renewal Date</u>
Texas	1986	Permanent	H0637	5/97

4. E.C.F.M.G.

n/a

5. Other:

Basic Cardiac Life Support - 1995

G. Honors and Awards

1996 Departmental Excellence in Research Award

1990-1992 Fellowship Award for Research, Agency for Toxic Substances and
Disease Registry, U.S. Public Health Service

1990	World Health Organization (WHO) Macedo Award, presented to the New Jersey Department of Health for the New Jersey Report on Chemical Sensitivity (co-author)
1985	Merck Award for Medical Scholarship, University of Texas Health Science Center, San Antonio, Texas
1974	President's Award for Excellence in Government Operations, U.S. Department of Labor
1968	Honors Degree in Molecular Biology, University of Wisconsin, Madison, Wisconsin
1967	Phi Beta Kappa, University of Wisconsin, Madison Wisconsin
1966	Sigma Epsilon Sigma, University of Wisconsin, Madison, Wisconsin

II. TEACHING

A. Classroom/Laboratory Teaching

10/96-Present	Third-year Family Practice Clerkship	MS/U	2 hrs/mo.	Instructor
7/96-Present	Environmental Medicine/ Border Health	MS/URG	144 hrs/mo.	Course Director
7/96	Epidemiology	MS/U	4 hrs	Instructor
2/96-5/96	Physical Diagnosis	MS/U	15 hrs	Instructor
7/95	Epidemiology	MS/U	7 hrs	Instructor
2/95-5/95	Physical Diagnosis	MS/U	15 hrs	Instructor
9/94	Advanced Physical Diagnosis	MS/U	1 hr	Instructor
10/94	Environmental Health School of Public Health	GS/GP	2 hrs	Instructor

8/94	Epidemiology	MS/U	4 hrs	Instructor
2/94-5/94	Physical Diagnosis	MS/U	15 hrs	Instructor
10/93	Environmental Health School of Public Health	GS/GP	2 hrs	Instructor
8/93	Advanced Physical Diagnosis	MS/U	1 hr	Instructor
11/92	Third-Year Family Practice Clerkship	MS/U	2 hrs	Instructor
10/92	Environmental Health School of Public Health	GS/GP	2 hrs	Instructor
8/91-6/92	Family Practice Specialty Conference	MS/R	6 hrs	Instructor

B. Clinical Teaching

<u>Date</u>	<u>Setting</u>	<u>Level</u>	<u>weeks per yr</u>	<u>hours per wk</u>
1/96-8/96	Family Practice Core Curriculum Conference	MS/R	2	1.5
4/96	Continuing Medical Education - Del Rio	MS/P	1	1
1/96-12/96	Occupational Medicine Residency Conference, USAF School of Aerospace Medicine	MS/P	6	2
11/95	Medicine Housestaff Conference	MS/R	1	1
11/95	Continuing Medical Education - Laredo	MS/P	1	1

3/95	Public Health Sciences School of Nursing	NS/P	1	3
1/95	Continuing Nursing Education	NS/P	1	3
1/95-12/95	Occupational Medicine Residency Conference School of Aerospace Medicine	MS/P	6	2
10/94	Psychiatry Grand Rounds	MS/URP	1	1
7/94	Continuing Nursing Education	NS/P	1	1
3/94	Continuing Medical Education, Family Practice Review Course and Workshop	MS/P	1	4
1/94	Dental School Grand Rounds	DS/UP	1	1
12/93	Continuing Medical Education, Allergy/ Immunology for Primary Care Practitioners	MS/P	1	1
3/93	Continuing Medical Education, Family Practice Review Course	MS/P	1	1
1991-1992	Allergy and Immunology Clinic	MS/UR	50	4

SCHOOL:

(MS) Medical School

(NS) Nursing School

(DS) Dental School

LEVEL:

(U) Undergraduate

(R) Resident

(G) Graduate

(P) Postgraduate

C. Instructional Development

1. Formal Study to Improve Teaching Abilities:

Distance Learning Workshop, Office of Educational Resources, UTHSCSA, August 8-9, 1996.

Health and the Environment, 2-day faculty development workshop for medical school educators, Consortium for Environmental Education in Medicine, San Antonio, Texas, June 27-28, 1996.

Departmental Faculty Development Workshops: OSCE's (2/96); Test Construction (1/96); Cultural Sensitivity (1/96); Team-building (12/95); Mentorship (1/95, 11/95).

Educating Physicians in Occupational Health and the Environment, 2-day faculty and curriculum development workshop, University of Massachusetts, Worcester, Massachusetts, June 4-5, 1992.

2. Current Research Concerning Teaching:

Development of Student Elective on Environmental Medicine and Border Health

Development of Residency Elective on Environmental Medicine and Border Health

3. Bibliography Concerning Teaching:

none

4. Media and Software Developed:

none

D. Masters' Theses and Ph.D. Dissertations Directed, Membership on Supervising Committees, and Postdoctoral Fellows Supervised:

none

III. RESEARCH

A. Bibliography

1. Books and Chapters

Chapter

Ashford NA, Miller CS: Chemical sensitivity and low level exposures: scientific and policy considerations. In *Quality of the Indoor Environment*. London, Lonsdale Press Ltd., 1992.

Book

Ashford NA, Miller CS: *Chemical Exposures: Low Levels and High Stakes*. New York, Van Nostrand-Reinhold, 1991.

2. Papers Published or In Press - Papers with asterisk (*) are refereed.

Miller CS: Toxicant-induced loss of tolerance: an emerging theory of disease? *Environmental Health Perspectives* (in press). *

Miller CS, Ashford NA, Doty R, Lamielle M, Otto D, Rahill A, Wallace L: Empirical approaches for the investigation of toxicant-induced loss of tolerance. *Environmental Health Perspectives* (in press).*

Ashford NA, Miller CS: Low-level chemical sensitivity: current reflections. *International Archives of Environmental Health* (in press).*

Miller CS: Chemical sensitivity: Symptom, syndrome or mechanism for disease? *Toxicology* 111:69-86, 1996.*

Overstreet DH, Miller CS, Janowsky DS, Russell RW: A potential animal model of multiple chemical sensitivity with cholinergic supersensitivity. *Toxicology* 111:119-134, 1996.*

Gammage RB, Miller CS, Jankovic JT: Exacerbation of chemical sensitivity associated with new construction: a case study. *Proceedings of Indoor Air '96*, 2:291-296, 1996.*

Bell IR, Miller CS, Schwartz GE, Peterson JM, Amend D: Neuropsychiatric and somatic characteristics of young adults with self-reported chemical odor intolerance and chemical sensitivity. *Archives of Environmental Health* 51(1):9-21, 1996.*

Sikorski EE, Kipen HM, Selner JC, Miller CS, Rodgers KE: Roundtable summary:

The question of multiple chemical sensitivity. *Fundamental and Applied Toxicology* 24:22-28, 1995.*

Miller CS, Mitzel HC: Chemical sensitivity attributed to pesticide exposure versus remodeling. *Archives of Environmental Health* 50(2):119-129, March-April, 1995.*

Ashford NA, Miller CS: Chemical sensitivity: An emerging public health and environmental problem. *Environmental Impact Assessment Review* 1994, 14:451-467, 1994.

Bell IR, Schwartz GE, Amend D, Peterson JM, Kaszniak AW, Miller CS: Psychological characteristics and subjective intolerance for xenobiotic agents of normal young adults with trait shyness and defensiveness: a Parkinsonian-like personality type? *Journal of Nervous and Mental Disorders* 182(7):367-374, 1994.*

Miller CS, Ashford, NA: The hypersusceptible individual. *Proceedings of Indoor Air '93*, 1:549-554, 1993.*

Miller CS, Ashford NA: Allergy and multiple chemical sensitivity distinguished. *Multiple Chemical Sensitivities: Addendum to Biologic Markers in Immunotoxicology*. Washington, D.C., National Academy Press, 1992.

Miller CS, Ashford NA: Possible mechanisms for multiple chemical sensitivities: the limbic system and others. *Multiple Chemical Sensitivities, Addendum to Biologic Markers in Immunotoxicology*. Washington, D.C., National Academy Press, 1992.

Miller CS: Possible models for multiple chemical sensitivity: conceptual issues and role of the limbic system. Advancing the Understanding of Multiple Chemical Sensitivity. Association of Occupational and Environmental Clinics. *Toxicology and Industrial Health* 8(4):181-202, 1992.*

Bell IR, Miller CS, and Schwartz, GE: An olfactory-limbic model of multiple chemical sensitivity syndrome: Possible relationships to kindling and affective spectrum disorders. *Biological Psychiatry* 32:218-242, 1992.*

Updike S, Miller CS, and Magnuson J: Immobilization in hypoallergenic gel: A method of protecting enzymes from proteolysis and antibody complexing. *Enzyme therapy in genetic diseases, Birth Defects Original Article Series* 9:2, 1973.

3. Abstracts

Prasad V, Brown RL, Miller CS, Luduena RF: Interaction of pyridostigmine bromide with bovine brain tubulin. *Molecular Biology of the Cell* 6 (Suppl.):29a, 1995.

Overhulser PI, Inglefield JT, Miller CS, Kniker WT (1991): Utility of oral cromolyn in food associated disease. *Annals of Allergy* 66(1):67, 1991.

4. Reviews and Editorials

Miller CS, Ashford NA: Chemical sensitivity: perspectives from North America and Europe. *Proceedings of Healthy Buildings '95*, 1:49-66.

Miller CS: White paper: chemical sensitivity: history and phenomenology. *Toxicology and Industrial Health* 10(4-5):253-276, 1994.*

Ashford NA and Miller CS: *Chemical Sensitivity: A Report to the New Jersey State Department of Health*. December, 1989.

5. Other

Letters-to-the-Editor

Miller CS: Multiple chemical sensitivity syndrome. *Journal of Occupational Medicine* 37(12):1323, 1995.

Invited Lectures and Presentations

Allergic and non-allergic mechanisms in building-related hypersensitivity reactions (invited plenary). Symposium on the Indoor Environment and Health, Vardal Foundation and the Allergy Program of the National Institute of Public Health, Stockholm, Sweden, November 6-8, 1996 (to be presented).

Invited testimony on low level nerve agent exposure and the Gulf War veterans' illnesses. Presented before the U.S. House of Representatives Committee on Government Reform and Oversight, Subcommittee on Human Resources and Intergovernmental Relations, September 19, 1996.

Exacerbation of chemical sensitivity associated with new construction: a case study (invited paper). Indoor Air '96 Nagoya, The 7th International conference on Indoor Air Quality and Climate, Nagoya, Japan, July 21-26, 1996.

Progress in understanding multiple chemical sensitivity (invited seminar). Indoor Air '96 Nagoya, The 7th International Conference on Indoor Air Quality and Climate, Nagoya, Japan, July 21-26, 1996.

Chemical sensitivity, the Gulf War veterans and the Sarin subway incident (invited lecture). Presented at Nippon Medical School to physicians who cared for victims of the Tokyo subway nerve agent exposure, Tokyo, Japan, July 19, 1996.

Health effects associated with exposure to low levels of volatile organic compounds (invited symposium). Presented at the American Industrial Hygiene Conference, Washington, D.C., May 23, 1996.

Indoor air pollutants and their health effects. Presented at the Environmental Protection Agency Course "Orientation to Indoor Air Quality," Austin, Texas, April 24, 1996 and Dearborn, Michigan, April 21-22, 1996.

Low-level chemical exposure (invited panel). Presented at the Texas Natural Resource Conservation Commission and the Middle Rio Grande Region Hazardous Waste and Substance Task Force Conference on "Preventing Health Risks Through Environmental Education," Del Rio, Texas, April 18, 1996.

Chemical sensitivity: new perspectives (invited lecture). Presented at the National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina, April 16, 1996.

Toxicant-induced loss of tolerance (invited lecture). Presented at the University of North Carolina School of Public Health, Chapel Hill, North Carolina, April 15, 1996.

Invited testimony on the Gulf War veterans' illnesses. Presented before the Presidential Advisory Committee on Gulf War Veterans' Illnesses, San Antonio, Texas, February 27, 1996.

Toxin-induced loss of tolerance: a new mechanism for disease? (invited panel). Presented at the Workshop on "Multiple Chemical Sensitivities (MCS)," International Programme on Chemical Safety, Berlin, Germany, February 21, 1996.

Effects of low-level environmental chemical exposures and relationship to pollution in border communities (invited lecture). Memorial lecture sponsored by the Laredo Community College, Texas A&M International University and the Tri-County Medical Society, Laredo, Texas, January 25, 1996.

Update on multiple chemical sensitivities (invited lecture). Presented at the American Industrial Hygiene Association Texas Hill Country Section meeting, San Antonio, Texas, January 11, 1996.

Multiple chemical sensitivity (invited lecture). Presented at the Chemical Specialties Manufacturers Association Environmental Affairs Conference, Annapolis, Maryland, October 26, 1995.

Toxin-induced loss of tolerance: an emerging theory of disease? (invited seminar). Presented at the Oxidant Stress and Antioxidant Seminar Series of the South Texas Chapter of the Oxygen Society, University of Texas Health Science Center at San Antonio, San Antonio, Texas, September 28, 1995.

Toxin-induced loss of tolerance (invited lecture). Presented at the National Institute of Environmental Health Sciences Superfund Basic Research Program and the Environmental and Occupational Health Sciences Institute Conference on Experimental Approaches to Chemical Sensitivity, Princeton, New Jersey, September 20, 1995.

Chemical sensitivity: perspectives from North America and Europe (invited plenary). Presented at Healthy Buildings '95, Milan, Italy, September 14, 1995.

Desert Storm "Syndrome" (invited lecture). Presented at the Department of the Army 807th Medical Brigade's Medical Conference, San Antonio, Texas, July 29, 1995.

Exposures and symptoms reported by Persian Gulf veterans in the Houston Regional Referral Center. Presented before the Department of Veterans Affairs Persian Gulf Expert Scientific Committee, Washington D.C., June 27, 1995.

Multiple chemical sensitivity: from sick buildings to the Gulf War (invited lecture). Presented at the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, June 19, 1995.

Conceptual basis for low-level chemical sensitivity (invited lecture). Presented at the Symposium on Low-level Chemical Sensitivity, Metropolitan Chapter of the Society for Risk Analysis, New York, New York, June 8, 1995.

The environmental medical unit: defining the role of environmental exposures in chronic illness (invited lecture). Presented at the Johnson Controls Institute for Environmental Quality in Architecture, University of Wisconsin, Milwaukee, Wisconsin, May 25, 1995.

Chemical sensitivity or chemophobia? (invited lecture). Presented at the S.C. Johnson Wax international officers' meeting, Racine, Wisconsin, May 24, 1995.

Chemical sensitivity: symptom, syndrome, or mechanism for disease? (invited lecture). Presented at the Agency for Toxic Substances and Disease Registry (U.S. Public Health Service) and Tri-service Conference on Risk Assessment Issues for Sensitive Human Populations, Wright-Patterson Air Force Base, Ohio, April 25, 1995.

Low-level environmental chemical exposures (invited lecture). Presented before the San Antonio Medical Foundation Board of Trustees, San Antonio, Texas, April 4, 1995.

Dealing with multiple chemical sensitivities (invited lecture). Ivey-Glass Memorial Speaker. Presented at the Texas Agricultural Extension Service Pest Control Workshop, Texas A&M University, College Station, Texas, January 4, 1995.

The chemical sensitivity syndrome: from sick buildings to the Gulf War (invited seminar). Presented at the University of North Carolina Center for Alcohol Studies and the Department of Psychiatry, Raleigh-Durham, North Carolina, November 28, 1994.

Multiple chemical sensitivity: recent developments (seminar). Presented at the San Antonio Risk Assessment and Toxicology Society, San Antonio, Texas, December 14, 1994.

Gulf War "Syndrome" (invited lecture). Office of Naval Research Distinguished Lecture Series, Arlington, Virginia, November 9, 1994.

An olfactory-limbic model of multiple chemical sensitivity syndrome (invited lecture). Presented at the Occupational Safety and Health '94 Conference, Toronto, Canada, October, 1994.

The effects of "low-level" environmental exposure on health (invited panel). Presented at the University of Texas System Texas-Mexico Border Health Symposium on Border Health Issues and NAFTA, South Padre Island, Texas, October 21, 1994.

Chemical sensitivity and the Gulf veterans (invited panel). Presented at the Wisconsin Persian Gulf Veterans Health Conference sponsored by the Department of Veterans Affairs, Madison, Tomah, Appleton and Milwaukee, Wisconsin, September 24-25, 1994.

Multi-system symptoms and loss of specific tolerance as features of environmental exposures (invited workshop). Presented at the Workshop on Temporomandibular Joint Alloplastic Implants and Local/Systemic Response: Observations and Research Needs, National Institute of Dental Research, National Institute of Arthritis and Musculoskeletal and Skin Diseases, Office of Research on Women's Health, and Food and Drug Administration, Bethesda, Maryland, September 12-13, 1994.

Multiple chemical sensitivity: the scientific basis (invited panel). Presented at the National Institutes of Health Technology Assessment Workshop on the Persian Gulf Experience and Health, Bethesda, Maryland, April 28, 1994.

What physicians should know about chemical sensitivity (invited keynote). Presented at Doctor's Day, Harrisburg, Pennsylvania, February, 1994.

Chemical sensitivity: history and phenomenology (invited plenary). White Paper presented at the Conference on Low-level Exposure to Chemicals and Neurobiologic Sensitivity, Agency for Toxic Substances and Disease Registry, U.S. Public Health Service, Baltimore, Maryland, April 6-7, 1994.

Research needs in chemical sensitivity. Presented at the workshop on Multiple Chemical Sensitivity: State of the Science, Annual Meeting of the American Public Health Association, San Francisco, California, October 24-28, 1993.

Multiple chemical sensitivity (invited lecture). Presented at workshop on aircraft cabin indoor air quality, Federal Aviation Administration, Oklahoma City, Oklahoma, September 28-30, 1993.

Challenges and opportunities in controlled human exposures (invited panel). Presented at Indoor Air '93, Helsinki, Finland, July 6, 1993.

Invited testimony on the health problems of Gulf War veterans. Presented before the Subcommittee on Oversight and Investigations of the Committee on Veterans' Affairs, U.S. House of Representatives, Washington, D.C., June 9, 1993.

Multiple chemical sensitivity -- what is it and does it exist? (invited panel). Presenter and roundtable participant at the American Industrial Hygiene Conference and Exposition, New Orleans, Louisiana, May 20, 1993.

Chemical sensitivity: clinical observations (invited keynote). Presented at the Workshop on Chemical Sensitivities and Their Relevance to Psychiatric/Psychologic Disorders, Health and Welfare Canada, Ottawa, Ontario, December 7, 1992.

Chemical sensitivity: clinical observations. Presented at the Annual Meeting of the American Public Health Association, Atlanta, Georgia, November 10-14, 1991.

Health Effects of Indoor Air (invited lecture). Presented at the EPA Region VI and Texas State Department of Health Indoor Air Quality Conference, Austin, Texas, 1991.

6. Papers Submitted

Mitzel HC, Miller CS: Attention and short term memory deficits among farmworkers in the Lower Rio Grande Valley.*

Nawab SS, Miller CS, Dale JK, Greenberg BD, Friedman TC, Straus SE, Chrousos GP, Rosenthal NE: Self-reported sensitivity to chemical exposures in five clinical populations and healthy controls.*

Miller CS: IPCS meeting on Idiopathic Environmental Intolerances, *Archives of Environmental Health* (letter-to-the-editor).*

B. Areas of Research Interest

Health Effects of Low Level Environmental Chemical Exposures
Texas/Mexico Border Environmental Health
Indoor Air Pollution
Gulf War Veterans' Illnesses
Use of an Environmental Medical Unit for Assessing Chemical Intolerances

C. Current Projects

Comparison of symptoms and sensitivities reported by multiple chemical sensitivity patients, implant recipients and Gulf War veterans

Development of a rodent model for xenobiotic sensitization

Implementation of a 1-month training elective in Environmental Medicine/Border Health in Laredo, Texas, for medical residents, medical and nursing students, and public health trainees

D. Research Support

National

Office of Naval Research
Rat Model for Sensitization to Xenobiotics
03/96 to 02/99
\$466,727
Principal Investigator

Agency for Toxic Substances and Disease Registry (U.S. Public Health Service)
Research Participation Program - ATSDR
01/94 to 06/94
\$12,000
Principal Investigator

Agency for Toxic Substances and Disease Registry (U.S. Public Health Service)
Clinical Research Fellowship in Environmental Medicine
07/90 to 06/92
\$53,300
Principal Investigator

State

South Texas/Border Region Education Initiative
South Texas Environmental Education and Research Center - Laredo (STEER)
09/95 to 08/97
\$442,013
Program Director

South Texas Health Research Center
A Pilot Study of Pesticide-related Illness in South Texas
09/92 to 08/93
\$22,000
Principal Investigator

University

Institutional Research Grant
Cognitive and Physiological Responses to Indoor Air Pollutants
09/92 to 08/93
\$8,000
Co-investigator

Other

none

IV. SERVICE

A. Professional Affiliations

1. Current Professional and Scientific Organizations and Societies - Organizations with asterisk (*) require election for membership.

1996-Present Texas Public Health Association

1995-Present International Society on Indoor Air Quality and Climate

1994-Present	San Antonio Risk Assessment and Toxicology Society
1992-Present	Association of Occupational and Environmental Clinics*
1992-Present	American Public Health Association
1990-1992	Texas Medical Association
1990-Present	American College of Allergy, Asthma and Immunology*
1990-Present	American Academy of Allergy, Asthma and Immunology*
1990-Present	San Antonio Allergy Society

2. Past and Current Positions and/or Offices Held in Professional Organizations

1991-1993	Appointed member, Committee on the Environment, Texas Medical Association
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3. Other Professional Activities

1996	Invited co-chair, technical session on Health Effects - Allergy, Indoor Air '96, Nagoya, Japan
1996	Invited co-chair, workshop on Progress in Understanding Multiple Chemical Sensitivity, Indoor Air '96, Nagoya, Japan
1996-Present	Invited member, Indoor Air Quality Task Force, Indoor Air Quality Branch, Texas Department of Health
1996	Invited participant, Workshop on Multiple Chemical Sensitivities (MCS), International Programme on Chemical Safety (UNEP-ILO-WHO), Berlin, Germany
1995-Present	Appointed member, National Toxicology Program Board of Scientific Counselors, Office of the Assistant Secretary for Health, Department of Health and Human Services
1995-Present	Reviewer, <i>Environmental Health Perspectives</i> , National Institute of Environmental Health Sciences

1995	Invited participant, Environmental Health Summit, Environmental Health Foundation and the National Institute of Environmental Health Sciences, Tucson, Arizona
1995	Invited participant and working group co-chair, Conference on Experimental Approaches to Chemical Sensitivity, National Institute of Environmental Health Sciences, Princeton, New Jersey
1994	Reviewer, <i>Inhalation Toxicology</i>
1994-Present	Invited member, Occupational Medicine Residency Advisory Committee, U.S. Air Force School of Aerospace Medicine
1994-1996	Appointed member, National Toxicology Program Board of Scientific Counselors Technical Reports Review Subcommittee Office of the Assistant Secretary for Health, Department of Health and Human Services
1994-1995	Invited session chair and member of planning committee, Agency for Toxic Substances and Disease Registry (U.S. Public Health Service) and Tri-Service Conference on Risk Assessment Issues for Sensitive Human Populations, Human Susceptibility, Wright-Patterson Air Force Base, Ohio
1994-Present	Reviewer, <i>Toxicology and Industrial Health</i>
1994	Appointed member, Panel on Developing a Research Protocol for Evaluating Individuals Reporting Sensitivities to Multiple Chemicals, California Department of Health Services, Berkeley, California
1994	Invited member of planning committee and author of conference white paper, Conference on Low Level Exposure to Chemicals and Neurobiologic Sensitivity, Agency for Toxic Substances and Disease Registry (U.S. Public Health Service)
1994	Reviewer, <i>Aerospace Medicine and Aviation</i>
1994	Reviewer, <i>Journal of the American Medical Association</i>
1993-Present	Appointed member (reappointed 1995), Department of Veterans Affairs Persian Gulf Expert Scientific Committee

- 1993 Appointed member, Advisory Panel on Environmental Illness - Multiple Chemical Sensitivity, Senate Subcommittee on the Rights of the Disabled, California State Legislature
- 1993 Invited member, Agency for Toxic Substances and Disease Registry (U.S. Public Health Service) Expert Panel - Multiple Chemical Sensitivity, Annapolis, Maryland
- 1992-1993 Appointed member, Advisory Board, Report to the Texas State Legislature on Occupational Injury and Illness in Texas
- 1992 Invited Participant, Workshop on Chemical Sensitivities and their Relevance to Psychiatric Disorders. Health and Welfare Canada (Mental Health Division, Health Services and Promotion Branch and Laboratory Center for Disease Control, Health Protection Branch), Ottawa, Ontario, Canada, December 7, 1992
- 1992 Invited member, Immune Test Battery Workshop, Agency for Toxic Substances and Disease Registry (U.S. Public Health Service), Atlanta Georgia
- 1991-1993 Invited member, Regional Indoor Air Quality Network, U.S. Environmental Protection Agency, Dallas, Texas
- 1991 Invited participant, Workshop on Multiple Chemical Hypersensitivity, National Research Council/National Academy of Sciences, Irvine, California
- 1991 Invited participant and member of planning committee, Association of Occupational and Environmental Clinics, Workshop on Chemical Sensitivity, Agency for Toxic Substances and Disease Registry, U.S. Public Health Service, Baltimore, Maryland
- 1990-1991 Invited member, EPA External Peer Review Panel for the EPA Indoor Air Quality and Work Environment Study, Environmental Protection Agency, Washington, D.C.
- 1990 Invited participant, Workshop on Environmental Hypersensitivity, Ontario Ministry of Health, Toronto, Ontario, Canada
- 1977-1981 Appointed member (reappointed 1979), National Advisory Committee for Occupational Safety and Health Office (NACOSH), Office of the Assistant Secretary of Labor

4. Community Activities

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| 1996-Present | Appointed Member, Environmental Task Force in Laredo, Advisory to the Texas Department of Health Office of Border Health, Laredo, Texas |
| 1994-Present | Member, Residency Advisory Committee, Occupational Medicine Residency, School of Aerospace Medicine, Brooks Air Force Base |
| 1994 | Advisor, East Side Environmental Group (Alamo Dome dirt), appointed by UTHSCSA President Howe, San Antonio, Texas |
| 1994 | Expert Panel Member, Wisconsin Persian Gulf Veterans Health Conference, Department of Veterans Affairs, Madison, Tomah, Appleton and Milwaukee, Wisconsin |

B. Patient Service

1. Inpatient

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| 1994-Present | Environmental and Occupational Medicine Consulting Physician, Audie Murphy VA Hospital, San Antonio, Texas |
| 1992-Present | Consulting Physician to the Chief of Staff, Houston VA Medical Center on Gulf veterans' illnesses |
| 1991-Present | Consulting Physician, Environmental and Occupational Medicine University Hospital, San Antonio, Texas |

2. Outpatient

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| 1991-Present | Consulting Physician, Environmental and Occupational Medicine University Clinic, University of Texas Health Science Center, San Antonio, Texas |
| 1991-1992 | Allergy/Immunology Outpatient Clinic |
| 1990-1991 | Private practice, San Antonio, Texas |

3. Other

none

C. Committees

Department

1994-1995 Member, Financial Strategic Planning Committee, Department of Family Practice

School

none

University

1995-Present Member, Institutional Intellectual Property Committee

1994-1995 Member, Energy Conservation Committee

1992-Present Member, Institutional Animal Care and Use Committee (IACUC)

Hospital

1995-1996 Co-chair, *Ad hoc* Latex Team appointed by the Drug Utilization Evaluation Committee to evaluate and make recommendations on latex hypersensitivity and latex use, University Hospital

D. Administrative Responsibilities

1. Department, Division, Clinical Service, Coordinator, etc.

1995-Present Director, South Texas Environmental Education and Research Center

1992-Present Director, Occupational Health Program, UTHSCSA

2. Staff and Personnel Currently Supervised

Environmental Hygienist/Sanitarian (Laredo, Texas)

Research Nurse (Laredo, Texas)

Administrative Assistant I (South Texas Initiative)

Administrative Assistant I (Occupational Health Program - technical direction)

Administrative Secretary

V. OTHER PERTINENT INFORMATION

A. Patent Applications

Method of Treating Skin Lesions by Evoking Cell-mediated Immune Response

Method of Increasing Drug Absorption

B. Advisor

1996 MSI, MSII (2 students)