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file Gulfwar

Toxicology and Industrial Health, Vol. 10, No. 4/5, 1994 253

WHITE PAPER: CHEMICAL SENSITIVITY: HISTORY AND PHENOMENOLOGY

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

HISTORICAL OVERVIEW

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

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

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

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

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

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

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

FEDERAL AGENCY INTEREST

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

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

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

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

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

OPPOSING VIEWS OF THE ILLNESS

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

Terms for the condition:

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

Terms patients use to describe themselves:

universal reactors
canaries
chemies

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

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

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

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

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

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

CLINICAL OBSERVATIONS AND PHENOMENOLOGY

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

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

TABLE 1. Proposed Case Definitions for Multiple Chemical Sensitivity

Ashford and Miller (1989):

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

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

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

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

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

Cullen (1987):

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

Nethercott et al. (1993):

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

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

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

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

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

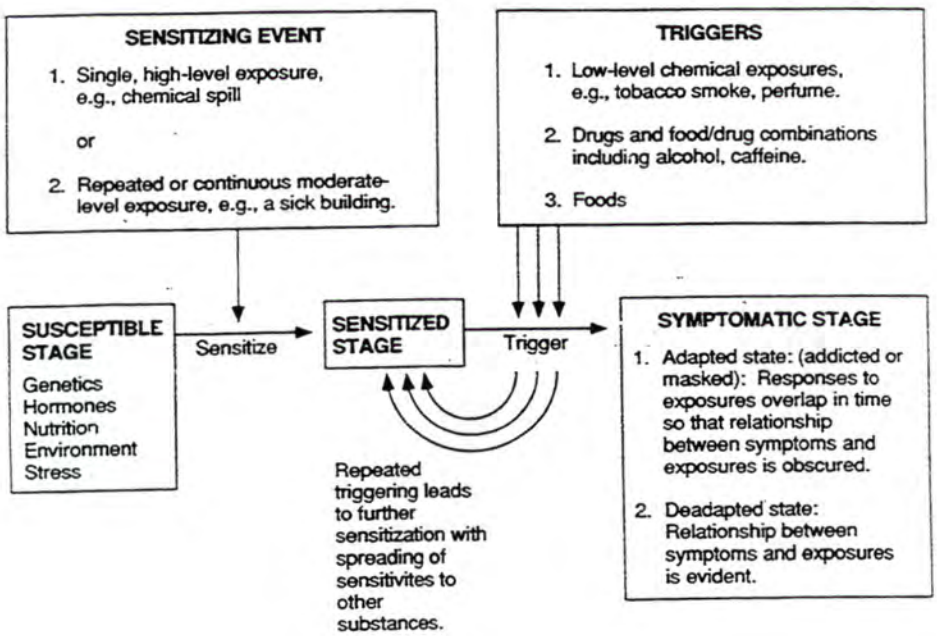

FIGURE 1. Phenomenology of Multiple Chemical Sensitivity.

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

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

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

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

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

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

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

Group	Nature of Exposure	Demographics
Industrial workers	Acute and chronic exposure to industrial chemicals	Primarily males; blue collar; 20 to 65 years old
Sick building occupants -	Off-gassing from construction materials, office equipment or supplies; tobacco smoke; inadequate ventilation	Females more than males; white-collar office workers and professionals; 20 to 65 years old; school children
Contaminated communities	Toxic waste sites, aerial pesticide spraying, groundwater and air contamination by nearby industry and other community exposures	All ages, male and female; children or infants may be affected first or most; pregnant women with possible effects on fetuses; middle to lower class
Individuals	Heterogeneous; indoor air (domestic), consumer products, drugs and pesticides	70–80% females; 50% 30 to 50 years old (Johnson and Rea, 1989); white, middle to upper middle class and professionals

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

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

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

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

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

PARALLELS WITH ADDICTION

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

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

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

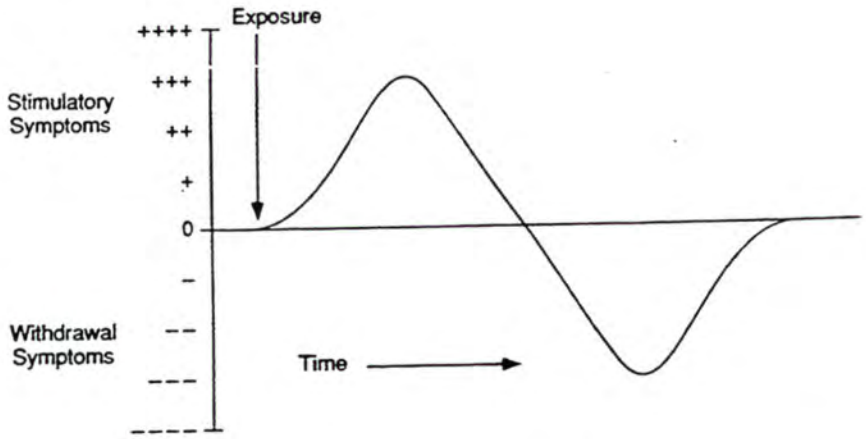

FIGURE 2. Graphical representation of symptom progression in a sensitive individual following exposure to a single substance (from O'Banion, Ecological and Nutritional Treatment of Health Disorders, 1981; courtesy of Charles C. Thomas, Publisher, Springfield, Illinois). The sine wave is a graphical representation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

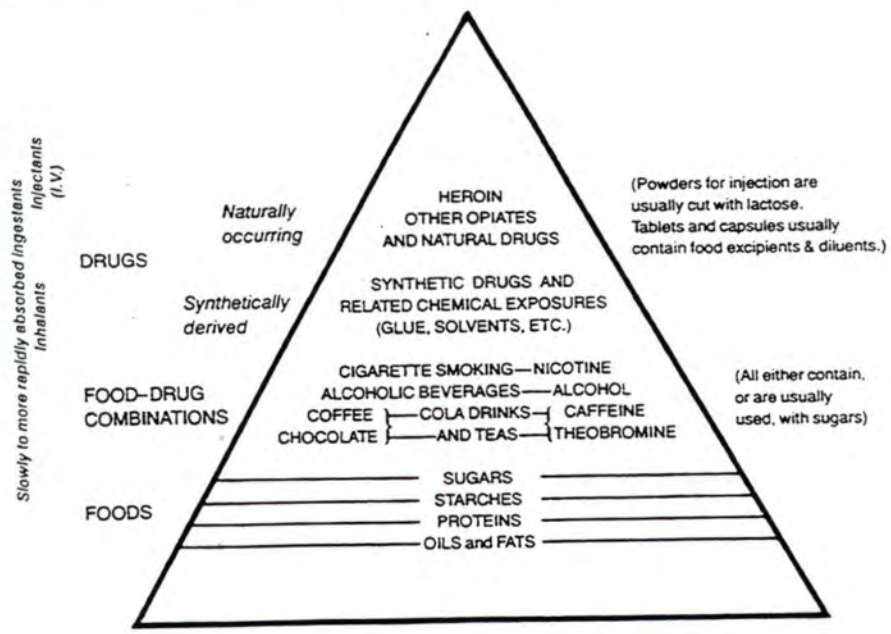

FIGURE 3. Addiction pyramid, after Randolph (1980).

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

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

SYMPTOMATOLOGY

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

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

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

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

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

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

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

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

SUMMARY OF RESEARCH AND RESEARCH RECOMMENDATIONS

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

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

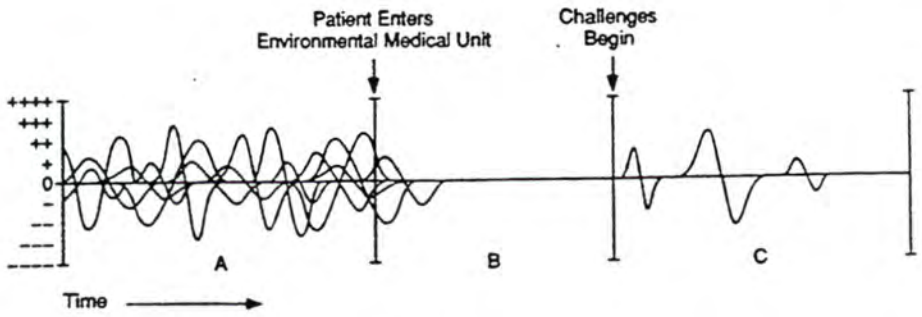

FIGURE 4. Hypothetical graphical representation of an individual's symptoms before and after entering an environmental unit (Ashford and Miller, 1991; © Van Nostrand Reinhold, 1991). In Time Period A, prior to entering an environmental medical unit (EMU), a chemically sensitive individual is responding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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

CONCLUSION

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

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

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

REFERENCES

AMERICAN ACADEMY OF ALLERGY AND IMMUNOLOGY. EXECUTIVE COMMITTEE OF THE AMERICAN ACADEMY OF ALLERGY AND IMMUNOLOGY (1986). "Position Statements — Clinical Ecology." J. Allergy Clin. Immunol. 78(8):269–271.

AMERICAN COLLEGE OF PHYSICIANS (1989). "Position paper: Clinical Ecology." Ann. Intern. Med. 111(2):168–178.

ASHFORD, N.A. and MILLER, C.S. (1989). Chemical Sensitivity. A Report to the New Jersey State Department of Health.

ASHFORD, N.A. and MILLER, C.S. (1991). Chemical Exposures: Low Levels and High Stakes. Van Nostrand Reinhold, New York.

ASSOCIATION OF OCCUPATIONAL AND ENVIRONMENTAL CLINICS (1992). Advancing the understanding of multiple chemical sensitivity. Toxicol. and Ind. Health. 8(4):1–257.

BASCOM, R. (1989). Chemical Hypersensitivity Syndrome Study: Options for Action, a Literature Review, and a Needs Assessment. A Report to the State of Maryland Department of Environment.

BELL, I.R., MILLER, C.S., and SCHWARTZ, G.E. (1992). "An olfactory-limbic model of multiple chemical sensitivity syndrome: Possible relationships to kindling and affective spectrum disorders." Biol. Psychiatry 32:218–242.

BRODSKY, C.M. (1987). "Multiple chemical sensitivities and other 'environmental illness': A psychiatrist's view." Occup. Med.: State Art Rev. 2(4):695–704.

CALIFORNIA MEDICAL ASSOCIATION TASK FORCE ON CLINICAL ECOLOGY (1986). "Clinical ecology: a critical appraisal." West. J. Med. 144(2):239–245.

CATHEBRAS, P.J., ROBBINS, J.M., KIRMAYER, L.J., and HAYTON, B.C. (1992). "Fatigue in primary care: Prevalence, psychiatric comorbidity, illness behavior, and outcome." J. Gen. Intern. Med. 7:276–286.

CULLEN, M.R., ed. (1987). "Workers with multiple chemical sensitivities." Occup. Med.: State Art Rev. 2(4):655–806.

DAUM, S. (1983). "Nitroglycerin and alkyl nitrates." In: Environmental and Occupational Medicine (W. Rom, ed.). Little, Brown and Co., Boston. pp. 639–648.

DOTY, R.L., DEEMS, D.A., FRYE, R.E., PELBERG, R., and SHAPIRO, A. (1988). "Olfactory sensitivity, nasal resistance, and autonomic function in patients with multiple chemical sensitivities." Arch. Otolaryngol. — Head Neck Surg. 114:1422–1427.

ENVIRONMENTAL PROTECTION AGENCY (1989). Report to Congress on Indoor Air Quality, Volume II. Assessment and Control of Indoor Air Pollution.

FIEDLER, N., MACCIA, C., and KIPEN, H. (1992). "Evaluation of chemically sensitive patients." J. Occup. Med. 34(5):529–538.

HACKNEY, J.D., KARUZA S.K., and LINN, W.S. (1977a). "Effects of ozone exposure in Canadians and southern Californians, evidence for adaptation?" Arch. Environ. Health 32:110–116.

HACKNEY, J.D., LINN, W.S., MOHLER, J.G., and COLLIER, C.R. (1977b). "Adaptation to short-term respiratory effects of ozone in men exposed repeatedly." J. Appl. Psychol. 43:82–85.

HUBER, P.W. (1991). Galileo's Revenge: Junk Science in the Courtroom. Basic Books, New York.

JOHNSON, A. and REA, W.J. (1989). Review of 200 cases in the Environmental Control Unit, Dallas, presented at the Seventh International Symposium on Man and His Environment in Health and Disease, February 25–26, Dallas, TX.

LEZNOFF, A. 1993. "Multiple chemical sensitivity: Myth or reality." Practical Allergy Immunol. 8(2):48–52.

MEGGS, W.J. and CLEVELAND, C.H. (1993). "Rhinolaryngoscopic examination of patients with the multiple chemical sensitivity syndrome." Arch. Environ. Health 48(1):14–18.

MILLER, C.S. (1992). "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. Toxicol. Ind. Health 8(4):181–202.

MILLER, C.S. and MITZEL, H.C. (1994). "Chemical sensitivity attributed to pesticide exposure versus remodeling." Arch. Environ. Health. In press.

NATIONAL RESEARCH COUNCIL (NRC) (1992). Multiple Chemical Sensitivities: Addendum to Biologic Markers in Immunotoxicology. National Academy Press, Washington, D.C.

NETHERCOTT, J.R., DAVIDOFF, L.L., CURB, W.B., and ABBEY, H. (1993). "Multiple chemical sensitivities syndrome: Toward a working case definition." Arch. Environ. Health 48(1):19–26.

O'BANION, D.R. (1981). Ecological and Nutritional Treatment of Health Disorders. Charles C. Thomas, Springfield.

RANDOLPH, T.G. (1987). Environmental Medicine — Beginnings and Bibliographies of Clinical Ecology. Clinical Ecology Publications, Inc., Fort Collins, CO.

RANDOLPH, T.G. and MOSS, R.W. (1980). An Alternative Approach to Allergies. Harper and Row, New York.

RIIHIMAKI, V. and SAVOLAINEN, H. (1980). "Human exposure to m-xylene. Kinectics and acute effects on the central nervous system." Ann. Occup. Hyg. 23:411–432.

SELNER, J.C. (1988). "Chemical sensitivity." In: Current Therapy in Allergy, Immunology and Rheumatology (L.M. Lichtenstein and A.S. Fauci, ed.). B.C. Decker, Inc., Philadelphia, PA. pp. 48–52.

SIMON, G.E., DANIELL, W., STOCKBRIDGE, H., CLAYPOOLE, K., and ROSENSTOCK, L. (1993). "Immunologic, psychological, and neuropsychological factors in multiple chemical sensitivity." Ann. Int. Med. 19(2):97–103.

SIMON, G.E., KATON, W.J., and SPARKS, P.J. (1990). "Allergic to life: Psychological factors in environmental illness." Am. J. Psychiatry 147:901–906.

STAUDENMAYER, H. and SELNER, J.C. (1987). "Post–traumatic stress syndrome (PTSS): Escape into the environment." J. Clin. Psychology 43(1):156–157.

TERR, A.I. (1986). "Environmental illness: A clinical review of 50 cases." Arch. Intern. Med. 146:145–149.

WALLACE, L., PELLIZZARI, E.D., and GORDON, S.M. (1985). "Organic chemicals in indoor air: A review of human exposure studies and indoor air quality studies." In: Indoor Air and Human Health (R. Gammage and S. Kaye, ed.). Lewis Publishers, Chelsea, MI. pp. 361–378.

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TOXICOLOGY

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

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).

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TOXICANT-INDUCED LOSS OF TOLERANCE
An Emerging Theory of Disease?

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Running head: Toxicant-induced Loss of Tolerance

Key words: adaptation
chemical sensitivity
masking
multiple chemical sensitivity
sensitivity
sensitization
tolerance
addiction
habituation

Abbreviations:

EMU: Environmental Medical Unit
TILT: Toxicant-induced loss of tolerance

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ABSTRACT

This paper attempts to clarify the nature of chemical sensitivity by proposing a theory of disease that unites the disparate clinical observations associated with the condition. Sensitivity to chemicals appears to be the consequence of a two-step process: (1) Loss of tolerance in susceptible persons following exposure to various toxicants, and (2) subsequent triggering of symptoms by extremely small quantities of previously tolerated chemicals, drugs, foods, and food/drug combinations including caffeine and alcohol. While chemical sensitivity may be the *consequence* of this process, a term that may more clearly describe the observed process is "toxicant-induced loss of tolerance." Features of this yet-to-be-proven mechanism or theory of disease which affect the design of human exposure studies include: (1) The stimulatory and withdrawal-like nature (resembling addiction) of symptoms reported by patients and (2) masking. Masking, which may blunt or eliminate responses to chemical challenges, appears to have several components: (1) Apposition, which is the overlapping of the effects of closely timed exposures, (2) acclimatization or habituation, and (3) addiction.

A number of human challenge studies in this area have concluded that there is no physiological basis for chemical sensitivity. However, these studies have failed to address the role of masking. To insure reliable and reproducible responses to challenges, future studies in which subjects are evaluated in an environmental medical unit, a hospital-based facility in which background chemical exposures are reduced to the lowest levels practicable, may be necessary. A set of postulates for determining whether there is a causal relationship between low level chemical exposures and symptoms using an environmental medical unit is offered.

INTRODUCTION

Clinical observations in North America (1-7) and Europe (8) point to an expanding group of patients who report sensitivities to extraordinarily low levels of environmental chemicals. This phenomenon, termed "chemical sensitivity" or "multiple chemical sensitivity," appears to develop de novo in some individuals following acute or chronic exposure to a wide variety of environmental agents including various pesticides, solvents, drugs, and air contaminants in "sick" buildings. Some practitioners have attributed a broad spectrum of chronic medical conditions involving any and every organ system to chemical sensitivity (Figure 1)(4).

Efforts to formulate a case definition for chemical sensitivity, to identify relevant biomarkers, and to explore a variety of mechanisms for the condition have escalated over the past decade. Several conflicting schools of thought have evolved with respect to underlying mechanisms, ranging from the purely psychological to the wholly physiological. In the midst of the tumult surrounding chemical sensitivity lies a profound but little-recognized scientific debate concerning the *origins* of disease. Some participants in this debate are challenging currently accepted notions concerning the causes for many chronic illnesses.

The purposes of this paper are: (1) To clarify the nature of chemical sensitivity by describing a general mechanism that appears to underlie these cases; (2) to propose a theory of disease based upon this general mechanism; and (3) to offer a set of testable postulates for corroborating or refuting this theory. Science afterall is not about opinion or belief. It is about "guess and test," that is, formulating hypotheses and then devising experiments to test them.

TERMINOLOGY

Phenomenologically, chemical sensitivity appears to develop in two stages (3,4): (1) Loss of tolerance (possibly, but not necessarily, due to sensitization) 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 (Figure 2). Although sensitivity to chemicals may be one of the *consequences* of this two-stage process, "chemical sensitivity" does not appropriately describe the *process* involved.

There are two principal reasons for this. First, while "chemical sensitivity" certainly sounds like an inconvenient problem to have, the words fail to convey the potentially disabling nature of the condition and its postulated origins in a toxic exposure. Some will balk at using the word "toxic" in this manner. However, numerous investigators from different geographic regions have published strikingly similar descriptions of individuals who report disabling illness following exposure to recognized environmental contaminants, albeit at levels not generally regarded as toxic (1, 9-12). Yet, *for these individuals,* the exposure appears to have been toxic.

Paracelsus aptly opined that dose makes the poison. However, as our knowledge has grown, it has become evident that *"dose + host"* makes the poison (for example, pack-years of smoking plus alpha-1-antitrypsin deficiency). Likewise, in the case of chemical sensitivity, not everyone exposed in a sick building or to a chemical spill develops chronic illness. It may thus be

concluded that individual susceptibility, whether physiological or psychological, must play a role in determining who gets sick. The term "chemical sensitivity" fails to convey this key observation that chemical exposures appear to *initiate* a process that results in chemical sensitivity. Conceivably, this phenomenon could represent a new type of toxicity.

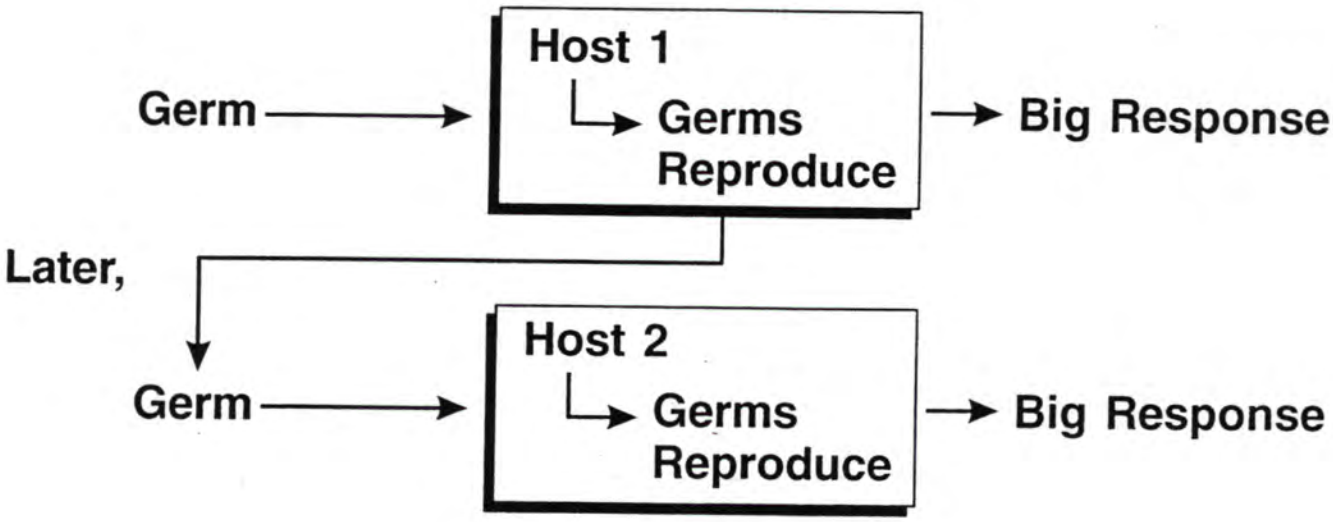
The second problem with the term "chemical sensitivity" is that it suggests that those afflicted become intolerant of *chemical exposures only*, when, in fact, caffeine, alcoholic beverages, various drugs, and foods reportedly trigger symptoms in these individuals once the process has been initiated (4, 12-15). For the above reasons, chemical sensitivity is a misnomer for the *process* under discussion. An alternative term, "toxicant-induced loss of tolerance" ("TILT"), has been proposed (16). This term offers several advantages. First, it describes the *process* as it has been observed by clinicians and patients. Second, it allows for the possibility that various toxicants may initiate the process. Third, it does not limit the resulting intolerance to chemicals. Finally, it sharpens the focus of the current debate over chemical sensitivity by positing a theory of disease that can be subjected to objective testing.

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, many of 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:

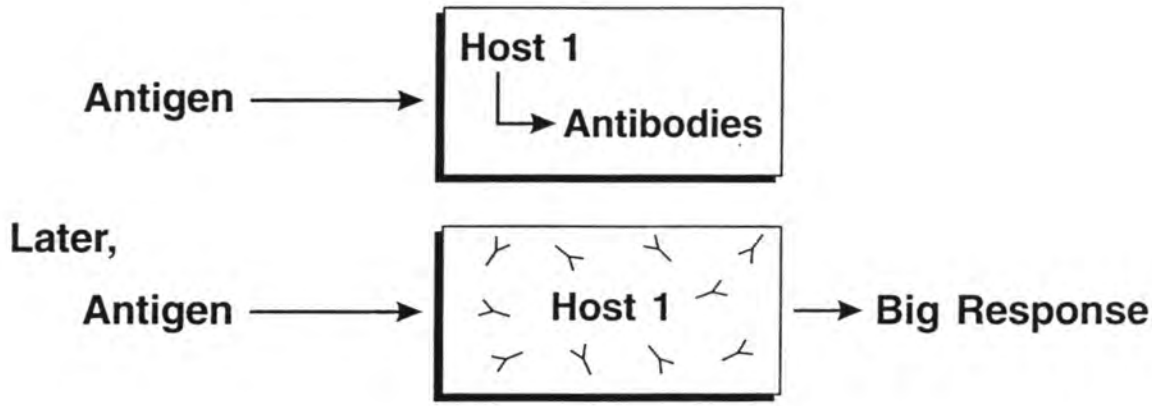
A theory of disease is a yet-to-be-established, general mechanism for a *class* or *family* of diseases. For the germ theory of disease, the boxes depicting the general mechanism of infection would look something like this:



Note that:

1. Many different kinds of germs cause responses.
2. There are many different responses involving any and every organ system (skin, respiratory, gastrointestinal)
3. *Specific* mechanisms vary greatly, for example cholera vs. AIDS vs. shingles.
4. There is no single biomarker; identification of specific germs took years.
5. Prevention (avoidance, antiseptics, sanitation, use of gloves) *preceded* knowledge of specific mechanisms.

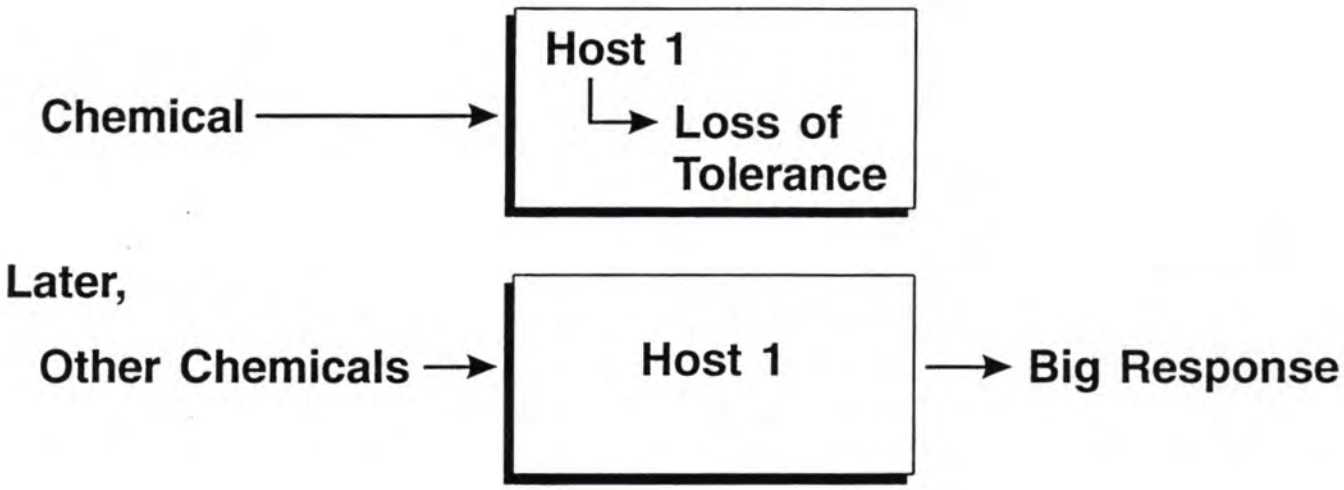
For the immune theory of disease, the boxes might look like this:



Here, just as for the germ theory of disease:

1. Many different kinds of antigens cause responses.
2. There are many different responses involving any and every organ system (skin, respiratory, gastrointestinal)
3. *Specific* mechanisms vary greatly, for example, poison ivy vs. allergic rhinitis vs. 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 toxicant-induced loss of tolerance, the boxes might look like this:



For toxicant-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. (16). Note that this

theory does not exclude the possibility that toxicant-induced loss of tolerance could turn out to be a special kind of toxicity or a variation on the immune theory of disease, just as allergy and delayed-type hypersensitivity are special cases that fall under the general classification of immunological disorders. A consequence of viewing TILT as a theory of disease would be a shift in perspective from chemical sensitivity as a syndrome to chemical sensitivity, now TILT, as a *class* of disorders, parallel to infectious diseases or immunologic diseases. Much effort has been devoted to developing a case definition for chemical sensitivity, with a singular lack of success. This lack of success would not be surprising if in fact TILT 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 or *all* immunological diseases.

Theories of 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 toxicant-induced loss of tolerance to either one of these theories, both of which have been widely corroborated, would be premature and presumptuous. On the other hand, toxicant-induced loss of tolerance has certain earmarks of an *emerging* theory of disease, including the vituperative professional disputes which surround it (16).

FEATURES OF TILT RELEVANT FOR ITS TESTING

As described by many investigators, this phenomenon appears to involve a two-stage process. Because of ethical considerations, the first stage (initiation) is more difficult to model in humans than the second stage (triggering). Ultimately, epidemiological studies and animal models may

elucidate the first stage. Fortunately, the second stage readily lends itself to testing via direct human challenges, a potent form of scientific evidence. However, in the design of human challenge studies in this area, certain key clinical observations must be taken into account. First, the commonly reported biphasic, stimulatory and withdrawal-like pattern of the patients' symptoms, particularly those symptoms involving the central nervous system must be understood in order to perform meaningful test challenges on these patients. Second, a related phenomenon called "masking" (to be described further) may "hide" responses to low level chemical challenges and therefore may need to be minimized prior to testing. Controlling masking may be analogous to controlling background noise in studies on sound.

The following sections will discuss these clinical features, their incorporation in experimental designs, and how failure to do so might threaten research outcomes.

STIMULATORY AND WITHDRAWAL SYMPTOMS

Theron Randolph first described the time course of the responses of these individuals to chemicals and foods (17). He reported striking parallels between their symptoms and those associated with alcohol and drug addiction. Randolph viewed the food and caffeine addictions his patients exhibited as the bottom rungs in a hierarchy of addiction, proceeding from foods and food/drug combinations such as caffeine and alcohol on the lower rungs, upward to nicotine and other naturally-occurring and synthetically-derived drugs (14).

Chemically sensitive patients resemble drug addicts in that members of both groups often report intense cravings and debilitating withdrawal symptoms. However, chemically sensitive patients' responses are not primarily to drugs. These individuals more commonly report addictions to caffeine or certain foods. While drug addicts manifest **ad**-dicted behaviors (L.*ad* "toward" + *dicare* "proclaim"), chemically sensitive patients respond as though they were **ab**-dicted (L.*ab* "away from" + *dicare* "proclaim") and assiduously *avoid* the very substances addicted persons favor, including alcohol, drugs, nicotine, and caffeine.

The stimulatory and withdrawal symptoms reported by chemically sensitive patients are frequently identical to those reported by normal persons exposed to much greater amounts of the same substances. For example, after drinking *one cup* of coffee, chemically sensitive patients may report feeling "hyper," jittery, talkative, nervous, anxious, or experiencing panic-like symptoms (stimulatory phase). Hours to days later, they may report withdrawal symptoms such as fatigue, yawning, confusion, indecisiveness, irritability, depression, loss of motivation, blurred vision, headaches, flu-like symptoms, hot or cold spells or heaviness in their arms and legs (withdrawal phase). Similar symptoms occur during caffeine withdrawal among some low-to-moderate caffeine users in the general population (18). Large numbers of chemically sensitive patients and many Gulf War veterans with unexplained illness report that *one drink* of an alcoholic beverage causes inebriation and/or a severe hangover (12, 15, 19). These augmented responses suggest that those afflicted have lost their prior natural or native tolerance for such exposures.

Early in their illness, prior to eliminating caffeine from their diets, many chemically sensitive patients report having consumed chocolate, coffee, tea, or cola addictively, often in very large quantities (15). Some carried large cups of coffee or tea around with them wherever they went. Many report later having stopped use of all caffeine and xanthines, generally on the advice of a friend or physician, and subsequently experiencing several days of intense withdrawal symptoms. Frequently they report that it was only after eliminating *all* xanthines from their diets that they were able to discern the effects of consuming a single cup of coffee or a chocolate bar. Most report becoming aware of the unpleasant effects of caffeine only after a trial of partial or complete caffeine avoidance. In this regard, chemically sensitive patients resemble certain reformed smokers or alcoholics who after quitting their addictants report extreme sensitivity to minute amounts of them. Terms like "addiction," "withdrawal," and "detox" pepper the vocabulary of chemically sensitive patients. One described the condition as being "like drug abuse without any of the fun." These parallels to addiction provide perspective: They may help explain why the mechanisms that underlie chemical sensitivity have been difficult to define and why biological markers have proven elusive.

In summary, drug addiction and toxicant-induced loss of tolerance share a number of features in common. TILT also has features reminiscent of toxicity and allergy (Table 1). However, it is its resemblance to addiction that is perhaps most striking and which has escaped the attention of many physicians and researchers.

MASKING

Suppose that toxicant-induced loss of tolerance was a mechanism underlying *certain* cases of chronic fatigue, migraine, asthma or depression. It might be reasonable to wonder why these patients do not also report chemical intolerances. In fact, some, but not all, do report them (21, 22). Many chemically sensitive patients carrying these same diagnoses say that it was not until they accidentally or intentionally avoided a sufficient number of their problem incitants that they noticed feeling better. Then, when they reencountered one of those incitants, robust symptoms occurred. As they repeated this iterative process of avoidance and re-exposure they noticed that particular symptoms occurred with particular exposures. Most indicate that had they not avoided *many* chemicals and foods simultaneously, or *"unmasked"* themselves, they would not have figured out what was making them sick.

"Masking" and "unmasking" are colorful lay terms for which there is no scientific equivalent. Nevertheless, investigators' ability to understand *masking* and *unmasking* and manipulate these variables knowledgeably may determine the success of studies in this area. When chemically sensitive patients follow a diet free of their problem foods and live in a relatively chemical-free home in the hills of central Texas where there are no major agricultural or industrial operations or air contaminants, they say they are in an "unmasked" state. Under these circumstances, if a diesel truck were to drive by, they claim they could identify specific symptoms due to the diesel exhaust, perhaps irritability, headache, or nausea.

On the other hand, the patients say that when they travel to a large city like Houston or New

York City, stay in a hotel room, and eat in restaurants, they become "masked." In the presence of many concurrent exposures (exhaust, fragrances, volatiles offgassing from building interiors, various foods) in New York City they feel chronically ill as if they had flu. If a diesel truck were to drive under these circumstances, they say they would not be able to attribute any particular symptoms to the exhaust. There would be too much "background noise" from overlapping symptoms occurring as a consequence of overlapping or successive exposures. In theory, such background noise or *masking* would hide the effect of individual exposures. Responses would blur together.

Masking appears to involve at least three interrelated components, any of which could interfere with the outcome of low level chemical challenges in these individuals: (1) Acclimatization, (2) apposition, and (3) addiction. In real life, these three components probably operate concurrently, although here they will be considered individually.

There is some notation that can be used to help depict these components. In the addiction literature, responses to addictive drugs are often illustrated graphically using a biphasic curve or sine wave (Figure 3). The portion of the sine wave above the horizontal axis represents symptoms with *onset* of exposure, often called "stimulatory" symptoms; the portion below represents symptoms with "*offset*" or cessation of exposure, often referred to as "withdrawal" symptoms. The height or amplitude of the sine wave in either direction is proportional to the severity of the response. For a person who is not sensitive to the substance, the curve would be a flat line, with zero amplitude in either direction. The length of the biphasic curve

represents the duration of symptoms following an exposure, reportedly ranging from minutes up to several days depending upon the exposure and the individual. Of course, the particular nature of the symptoms would vary from one sensitive subject to the next and from substance to substance.

Suppose that some researchers wished to test a putatively sensitive subject by exposing him to a low concentration of xylene. Xylene is a common indoor air contaminant and a component of Molhave's mixture (23) which has been used in human inhalation challenge studies. How would they insure that their subject was unmasked (responses at true baseline) prior to challenge? The following components of masking would need to be considered and controlled:

1. **Acclimatization.** With continuous or repeated exposure to many environmental stressors, adaptation occurs. That is, symptoms diminish as exposure continues. Chemically sensitive patients' symptoms also decrease with continuing exposure, however, in their case when the exposure ceases they often report marked withdrawal symptoms. Thus, what they describe is more akin to *habituation*, than to adaptation. Suppose further that the subject who is to be challenged with xylene works in a sick building where he routinely is exposed to low levels of xylene on a regular basis. If he is administered a test exposure to xylene below the odor threshold (0.62 ppm) (24), it may produce little or no effect if he has been working in that building during the preceding week (Figure 4). On the other hand, if he were to avoid the building and all other sources of xylene for 4 to 7 days before testing, a more robust response to the xylene challenge might be anticipated.

Thus, a sensitive subject's response to a challenge may range widely in intensity, from none to maximal, depending upon how recently that person has been exposed to the test substance or a chemically-related substance. If insufficient time has elapsed, for example, less than 4 days, the challenge may yield a falsely negative response as a result of habituation. If too much time has elapsed, for example, weeks or months, sensitivity may have waned.

2. **Apposition.** Suppose next that the research subject is sensitive to multiple substances. On the day he is scheduled for challenge testing, he gets up in the morning, uses some scented soap or hairspray, cooks breakfast on a gas stove, and drives his car through heavy traffic to get to the laboratory. Inside the laboratory building he rides an elevator where he is exposed to people wearing various colognes. If he were sensitive to several of these exposures, his responses might overlap in time. Such responses reportedly can last for hours or days. If so, they could persist during a placebo challenge, resulting in a false positive response. Thus, *apposition* or *juxtaposition* of the effects of closely timed exposures, is a second component of masking that must be controlled prior to and during challenge studies (Figure 5).

3. **Addiction.** Many of the symptoms chemically sensitive patients report mirror those commonly associated with addiction. Addiction itself may be a component of masking. Addicted individuals consciously or subconsciously time their next "hit" so as to forestall withdrawal symptoms (Figure 6), a phenomenon recognized to occur in alcohol, tobacco, and caffeine addiction. However, addiction to *foods* also is reported among chemically sensitive patients. Randolph described wheat, eggs, milk and corn as the most common addictants in his

patients (14, 17). Frequently, these individuals report intense cravings and consume astounding quantities of foods, for example, a pound of chocolate, several bags of popcorn, a dozen doughnuts, or 30 cups of coffee in one day. Patients most often report this kind of addictive consumption early in their illness, prior to the time they practiced avoiding problem exposures.

Foods may contain bioactive constituents such as tyramine, monosodium glutamate, and opiates (13). Persons who routinely use tobacco, caffeine, alcohol, or foods containing bioactive substances may need to avoid these prior to testing because the pharmacologic effects of these agents could override or mask the effect of an experimental challenge. Failure to eliminate addictants before testing could result either in false positive challenges due to lingering symptoms from an addictant used in the hours or days preceding a placebo challenge or in false negative challenges due to masking by an addictant.

TESTING THE TILT THEORY

After the germ theory of disease was introduced in the late 1800's, many overly enthusiastic investigators who were careless in their bacteriological technique announced that they had discovered the causative agents for tuberculosis, yellow fever, and other diseases. These pronouncements and subsequent retractions became so frequent that in 1884 the President of the New York Academy of Medicine lamented that a "bacteriomania" had swept over the medical profession (25). In order to prevent future such pseudo-discoveries, Koch, who identified the organisms responsible for tuberculosis, anthrax, and cholera, proposed a set of rules for etiological verification. Koch's postulates required that: (1) The microbe must 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; and (4) the microbe must be recoverable from the inoculated animal and be able to be grown again.

Just as bacteriomania engulfed the medical profession in the 1880's, "chemomania" is poised to engulf it now. Chemical sensitivity is in need of a set of postulates to ensure that future causal determinations are scientifically based. Figure 7 illustrates the following set of postulates which, if met, would confirm (and if not met, refute) that a person's symptoms were caused by a particular substance:

1. When a subject simultaneously avoids all chemical, food and drug incitants, remission of symptoms occurs (unmasking).
2. A specific constellation of symptoms occurs with re-introduction of a particular incitant.
3. Symptoms resolve when the incitant is again avoided.
4. With re-exposure to the same incitant, the same constellation of symptoms reoccurs, provided that the challenge is conducted within an appropriate window of time. Clinical observations suggest that an ideal window is 4 to 7 days following the last exposure to the test incitant.

In order to apply these postulates, the timing of exposures and degree of masking should be

rigorously controlled. To accomplish this, a hospital-based clinical research facility called an "environmental medical unit" (EMU) would be needed in order to isolate subjects from background exposures (Figure 8)(4, 5, 15, 16, 26). The EMU would be constructed, furnished, and operated so as to minimize exposure to airborne chemicals. For example, no disinfectants, perfumes, or pesticides would be allowed in the unit. Ventilation would maximize fresh outside air, and provide optimal particulate and gas filtration. Patients would eat chemically-less-contaminated foods and water, testing one food per meal in order to determine the effects of individual foods. If symptoms persisted despite this approach, fasting for a few days would be attempted prior to re-introduction of single foods.

The rationale for housing subjects in an environmentally-controlled facility for several days prior to challenges is twofold: (1) To prevent extraneous exposures to inhalants or ingestants so that responses to them are not misconstrued as positive responses when placebo challenges are administered (false positives), and (2) to minimize masking that might blunt or eliminate responses to active challenges (false negatives).

Although the terms "exposure chamber" and "environmental medical unit" sound similar, conceptually they differ in important ways:

1. *Patient Safety*. By definition, an environmental medical unit is in a *hospital* where patients can remain 24 hours a day in a clean environment for up to several weeks. Like an intensive care unit or coronary care unit, the environmental

medical unit would be a specialized, dedicated hospital facility. The EMU must be in a hospital in order to accommodate very sick patients. Exposure chambers do not offer a comparable level of care. Because chemical challenges may precipitate bronchoconstriction, mental confusion, severe headaches, depression, and other disabling symptoms, these patients should not be tested in an exposure chamber on an outpatient basis.

2. *Control of interfering exposures*. Conventional exposure chambers do not reduce background chemical exposures for extended periods (up to several weeks) so that the effects of a particular challenge in a patient can be assessed accurately. This is the central limitation of chambers and the reason why they should not be used to rule in or rule out chemical sensitivity. If subjects are not kept in a clean environment for several days prior to and during challenges, false positive responses due to interfering exposures and false negative responses due to masking may occur. In contrast with an exposure chamber, an environmental medical unit would minimize interfering exposures before and during challenges thus maximizing the *reliability* and *reproducibility* of test responses.

Availability of an EMU would allow physicians to refer a wide variety of cases in which environmental sensitivities were suspected to the unit for definitive evaluation. There, physicians could observe first-hand whether a 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 reintroduced 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, and provide inadequate separation from background exposures prior to challenges.

An analogy may help to illustrate the importance of controlling exposures for extended periods prior to challenge. If one wished to determine whether headaches in a coffee drinker 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 low concentration of a chemical might not produce any noticeable effect. On the other hand, if he were to remain in a clean environment such as an EMU for a few days before being tested *and* his condition improved, one could then perform meaningful challenges.

Placing patients in an EMU would simultaneously control all three components of masking: Stopping all exposures several days prior to challenge testing and spacing test exposures 4 to 7 days apart would preclude *acclimatization* or *habituation*; eliminating background chemical noise

and allowing the effects of each challenge to play out before introducing the next one would control *apposition*; and excluding drugs, alcohol, nicotine, and caffeine and spacing individual foods 4 to 7 days apart would interrupt any *addiction*. Individual sensitivity could then be evaluated in the EMU following the previously stated set of postulates for etiological verification (Figure 7).

For research purposes, challenges need to be performed in a double-blind, placebo-controlled manner. Patients with chronic fatigue syndrome, migraines, seizures, depression, asthma, or unexplained illnesses such as the Persian Gulf War veterans' illness could also be tested for sensitivities in an EMU using these postulates. Thus, the EMU could be used to determine whether or not particular patients with these diagnoses had a *forme masquée* of this illness.

What evidence is there that unmasking patients in an environmental medical unit and conducting challenges within a 4- to 7-day window of time is either useful or necessary? Thousands of credible patients and dozens of physicians have attempted this maneuver. They report that patients' symptoms resolve within a few days after they enter such a facility and that robust symptoms occur when challenges are conducted after several days of avoidance. Other evidence corroborates these observations: Withdrawal symptoms of several days' to a week's duration are known to occur in some persons following cessation of exposure to nitroglycerine (dynamite workers' headaches) (27); caffeine (18, 28); nicotine; and alcohol. Note that these are chemically *unrelated* substances. In individuals chronically exposed to xylene (29) or ozone (30), re-exposure following several days' avoidance results in robust symptoms. Foods may

require one to several days to navigate the digestive tract before they are eliminated. Taken together, these observations suggest that individuals with sensitivities to multiple incitants might experience effects that could linger as long as several days following avoidance. Thus, it may be argued that patients should be removed from their entire background of food and chemical exposures for 4 to 7 days prior to challenges, as Randolph first proposed (14, 17).

While it can be argued that synergistic or additive chemical combinations may be necessary to reproduce certain symptoms, this is a limitation of any form of challenge testing. Wherever possible, within the bounds of safety and feasibility, chemical combinations believed to precipitate the most robust and measurable responses should be explored. However, forty years of clinical observations, while anecdotal, suggest that single test substances may suffice for the majority of sensitive subjects. Confirmation or refutation of these claims seems a logical first step that should precede testing of complex mixtures. Finally, because isolating patients in a hospital environment like the EMU may have unanticipated psychological consequences, early studies in this area should examine the responses of control subjects in the same environment.

Conclusion

Good pathological and physiological theories provide "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...." (31). Theories and experiments that overlook salient observations or do not control experimental conditions adequately may lead to erroneous conclusions. During the late 19th Century, researchers collected sputum from patients with

tuberculosis, but were unsuccessful in culturing any organism. Some concluded that tuberculosis was not an infectious disease. These early investigators did not know that the tuberculin bacillus was fastidious and would grow out only after many weeks on a specialized culture medium. Correspondingly, scientists' ability to observe and understand chemical sensitivity may depend upon optimization of experimental conditions, that is, appropriate timing of challenges and use of an environmental medical unit for unmasking patients. To date, studies in this area have failed to unmask patients prior to challenge. When false positive and false negative responses occurred, the investigators concluded that chemical sensitivity was psychogenic in origin (32, 33).

In summary, features of toxicant-induced loss of tolerance overlap those of allergy, addiction and classical toxicity, yet TILT may be distinct from each of these. TILT appears to involve a two-step process (resembling allergic sensitization) in which persons lose specific tolerance (resembling addiction) for a wide range of common substances following a chemical exposure event (resembling toxicity). Just as the germ theory describes a class of diseases sharing the general mechanism of infection, the TILT theory of disease posits a class of chemically-induced disorders characterized by loss of tolerance to chemicals, foods, drugs and food/drug combinations. In the same way that fever is a symptom commonly associated with infectious diseases, chemical sensitivity may be a symptom associated with the TILT family of diseases. While clinical case definitions have been developed that describe particular infectious diseases, no clinical case definition can be applied to the *entire class* of infectious diseases. The same may be true for TILT disorders. The fact that this phenomenon does not fit already accepted

mechanisms for disease is often offered as evidence that the condition does not exist. However, the same criticism applied equally well to the germ and immune theories of disease when they first were proposed. *What is plausible depends upon the biological knowledge of the time* (34).

Looking to the future, carefully conducted epidemiological studies and animal models likely will play an important role in characterizing the initiation stage of TILT during which tolerance is lost. In the meantime, rigorous testing of the second stage of TILT, that is, the *triggering* of symptoms by tiny doses of chemicals, foods, drugs, caffeine or alcohol, is needed if progress in this area is to occur. Adoption of a set of relevant, testable hypotheses for etiological verification will serve to ensure the credibility of those endeavors.

> The mind likes a strange idea as little as the body likes a strange protein and resists it with similar energy. It would not perhaps be too fanciful to say that a new idea is the most quickly acting antigen known to science. If we watch ourselves honestly, we shall often find that we have begun to argue against a new idea even before it has been completely stated.
>
> Wilfred Trotter, English Philosopher/Scientist (1941)

REFERENCES

1. Cullen MR (ed.). Workers with multiple chemical sensitivities. Occup Med: State Art Rev 2(4):655-806 (1987).

2. Bascom R. Chemical Hypersensitivity Syndrome Study: Options for Action, a Literature Review, and a Needs Assessment. A Report to the State of Maryland Department of Environment (1989).

3. Ashford NA, Miller CS. Chemical Sensitivity. A Report to the New Jersey State Department of Health (1989).

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

5. National Research Council. Multiple Chemical Sensitivities: Addendum to Biologic Markers in Immunotoxicology. Washington, D.C.: National Academy Press (1992).

6. Association of Occupational and Environmental Clinics. Advancing the understanding of multiple chemical sensitivity. Toxicol Ind Health 8(4):1-257 (1992).

7. Thomson G. Report of the Ad Hoc Committee on Environmental Hypersensitivity Disorders. Ontario, Canada (1985).

8. Ashford N, Heinzow B, Lütjen K, Marouli C, Mølhave L, Mönch B, Papadopoulos S, Rest K, Rosdahl D, Siskos P, Velonakis E. Chemical Sensitivity in Selected European Countries: An Exploratory Study. Ergonomia Ltd. Athens, Greece (1994).

9. Cone JE, Sult TA. Acquired intolerance to solvents following pesticide/solvent exposure in a building: a new group of workers at risk for multiple chemical sensitivities? Toxicol Ind Health 8(4): 29-39 (1992).

10. Rosenthal N, Cameron CL. Exaggerated sensitivity to an organophosphate pesticide (letter). Am J Psychiatry 148(2): 270 (1991).

11. Ziem GE. Multiple chemical sensitivity: Treatment and followup with avoidance and control of chemical exposures. Advancing the understanding of multiple chemical sensitivity. Association of Occupational and Environmental Clinics. Toxicol Ind Health 8(4): 181-202 (1992).

12. Miller CS, Mitzel HC. Chemical sensitivity attributed to pesticide exposure versus remodeling. Arch Environ Health 50(2): 119-129 (1995).

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

14. Randolph TG, Moss RW. An Alternative Approach to Allergies. New York: Lippincott and Crowell (1980).

15. Miller CS (1992). 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. Toxicol Ind Health 8(4): 181-202 (1992).

16. Miller CS. Chemical sensitivity: Symptom, syndrome or mechanism for disease? Toxicol (in press).

17. Randolph TG. Human Ecology and Susceptibility to the Chemical Environment. Springfield, Ill.: Charles C Thomas (1962).

18. Silverman K, Evans SM, Strain EC, Griffiths RR. Withdrawal syndrome after the double-blind cessation of caffeine consumption. N Engl J Med 327(16): 1109-1114 (1992).

19. Miller CS. Multiple chemical sensitivity and the Gulf War Veterans. Presented at The Persian Gulf Experience and Health, NIH Technology Assessment Workshop, Bethesda, MD, April 27-29, 1994.

20. Waddell WJ. The science of toxicology and its relevance to MCS. Reg Toxicol Pharmacol 18: 13-22 (1993).

21. Kipen HM, Hallman W, Kelly-McNeil K, Fiedler N. Measuring chemical sensitivity prevalence: A questionnaire for population studies. Am J Public Health 85(4): 574-577.

22. Buchwald D, Garrity D. Comparison of patients with chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivities. Arch Intern Med 154: 2049-2053 (1994).

23. Mølhave L, Bach B, Pederson OF. Human reactions to low concentrations of volatile organic compounds. Environ Int 12: 167-175 (1986).

24. American Industrial Hygiene Association (AIHA). Odor Thresholds for Chemicals with Established Occupational Health Standards. Fairfax, VA: AIHA (1989).

25. Warner M. Hunting the Yellow Fever germ: The principle and practice of etiological proof in late nineteenth-century America. Bull Hist Med 59: 361-382 (1985).

26. Miller CS. White paper: Chemical sensitivity: History and phenomenology. Toxicol Ind Health 10(4/5): 253-276 (1994).

27. Daum S. Nitroglycerin and alkyl nitrates. In Rom W.(ed.) Environmental and Occupational Medicine. Boston: Little, Brown and Co. 1013-1019 (1992).

28. Griffiths RR, Woodson PP. Caffeine physical dependence: a review of human and laboratory animal studies 94: 437-451 (1988).

29. Riihimaki V, Savolainen K. Human exposure to m-xylene. Kinetics and acute effects on the central nervous system. Ann Occup Hygiene 23: 411-432 (1980).

30. Hackney J. et al. Effects of ozone in Canadians and Southern Californians, evidence for adaptation? Arch Environ Health 32(3): 110-116 (1977).

31. Carter KC. Ignaz Semmelweiss, Carl Mayrhofer, and the rise of the germ theory. Med Hist 29: 33-53 (1985).

32. Leznoff A. Multiple chemical sensitivity: Myth or reality. Practical Allergy Immunol 8(2): 48-52 (1993).

33. Staudenmayer H, Selner JC, Buhr MP. Double-blind provocation chamber challenges in 20 patients presenting with "multiple chemical sensitivity." Reg Toxicol Pharmacol 18: 44-53 (1993).

34. Hill AB. The environment and disease: Association or causation? Proc Royal Soc Med 58: 295-300 (1965).

Table 1. Features of Toxicant-Induced Loss of Tolerance Compared with Features of Addiction, Allergy and Toxicity

Feature	Toxicant-induced Loss of Tolerance[1]	Addiction[1]	Allergy[1]	Toxicity[1]
Chemical/drug intolerance	+	+	+	+
Ambient air incitants	+		+	+
Food intolerance	+		+	+
Alcohol intolerance	+	+		
Caffeine intolerance	+	+		
Withdrawal symptoms	+	+		
Craving, binging	+ (foods)	+ (drugs)		
Sensitization	+		+	
Induction by chemicals	+		+[2]	+
Induction by biologicals			+	
Multi-system symptoms	+	+	+	+
Frequent CNS symptomatology	+	+		+
Well-defined mechanism(s)			+	+
Genetic susceptibility	+	+	+	+
Dose/response relationship	+[3]		+[3]	+

[1]Categories 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.

[2]Low molecular weight chemicals may combine with tissue proteins producing "haptens" which evoke immune responses.

[3]Dose-response does occur for allergens: With the first, sensitizing exposure in 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 (20). The same kind of dose-response relationship may pertain for TILT, but has not been tested. Chemically sensitive individuals generally report increasingly severe symptoms the longer they remain in an exposure situation, an observation which suggests a dose-response relationship.

FIGURE 1. Some conditions that have been attributed to chemical sensitivity.

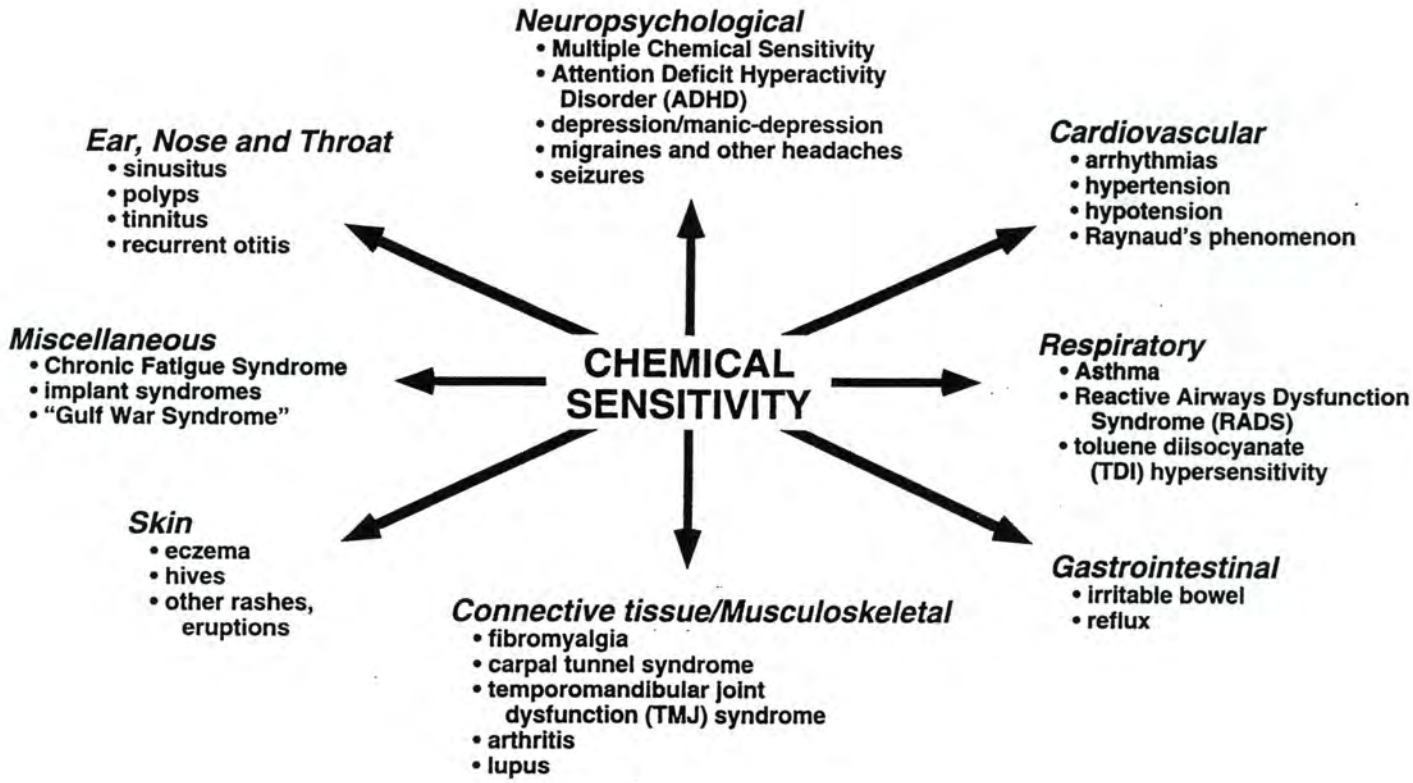


FIGURE 2. Phenomenology of chemical sensitivity. Chemical sensitivity appears to develop in two stages: (1) Loss of specific tolerance following acute or chronic exposure to various environmental agents, such as pesticides, solvents or contaminated air in a sick building, and (2) subsequent triggering 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.

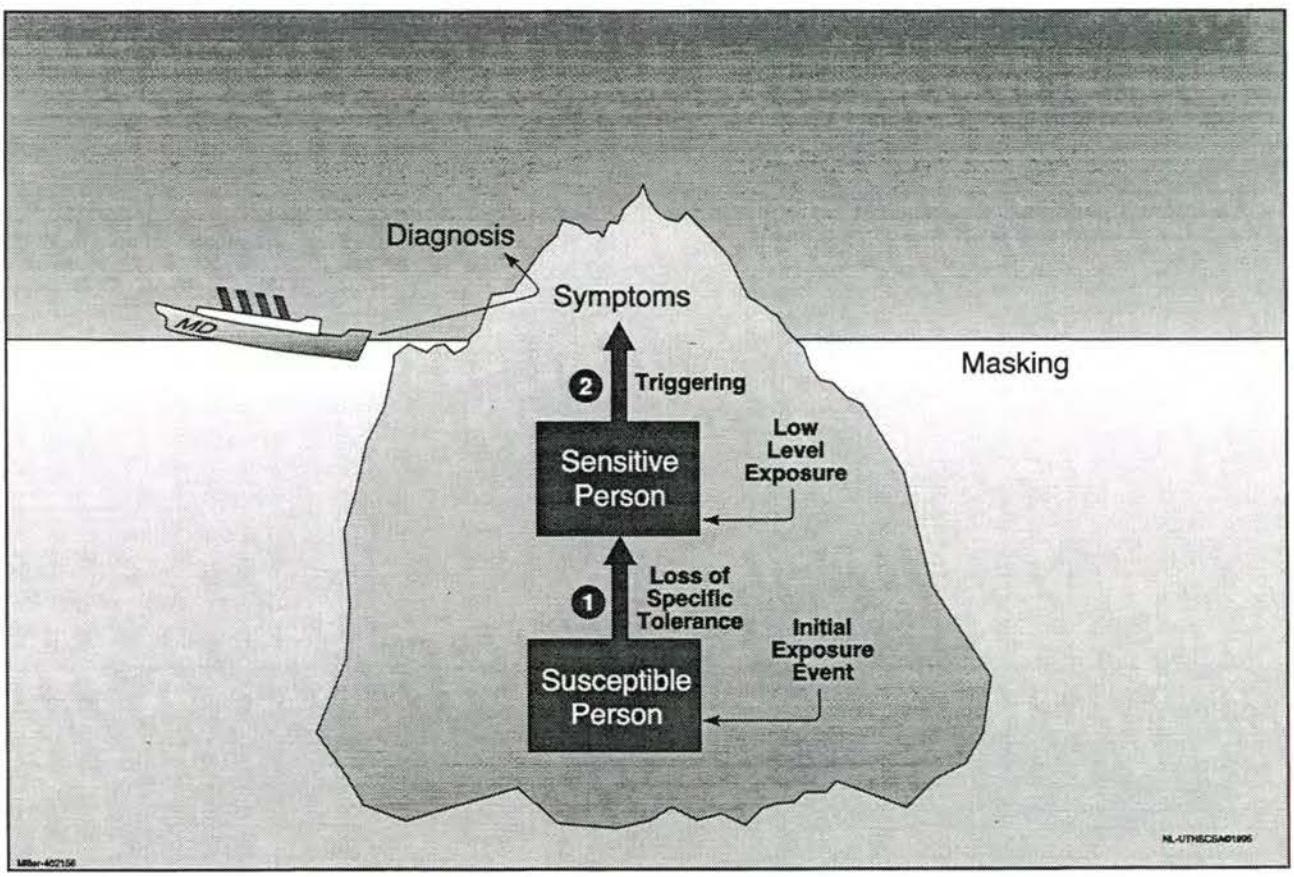


FIGURE 3. Graphical representation of symptom progression following exposure to single substance in a person sensitive to that substance (e.g., caffeine, a solvent, alcohol, nicotine). The portion of the biphasic curve above the line represents symptoms with onset of exposure (stimulatory symptoms) and the portion below, symptoms with offset of exposure (withdrawal symptoms). Amplitude is proportional to symptom severity. The length of the curve (duration of symptoms) may range from minutes to days.

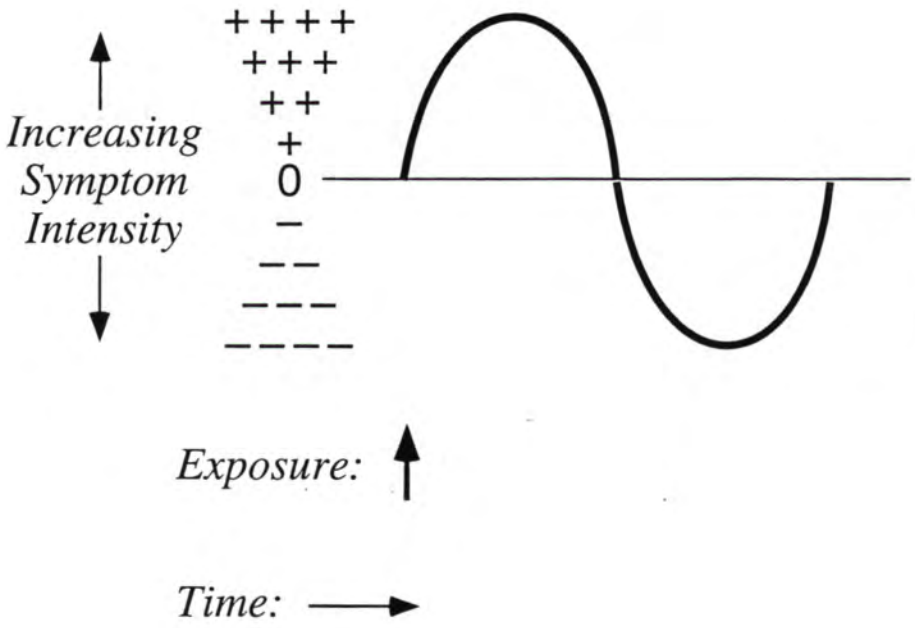


FIGURE 5. Apposition. If an individual is sensitive to many different substances, then the *effects* of everyday exposures to chemicals, foods or drugs may overlap in time. This apposition of effects might yield an individual who feels bad most of the time, but the effect of any single exposure is not apparent to either the individual or his physician. Apposition would tend to mask the effect of interest (solid lines) in much the same way that background noise masks a sound of interest.

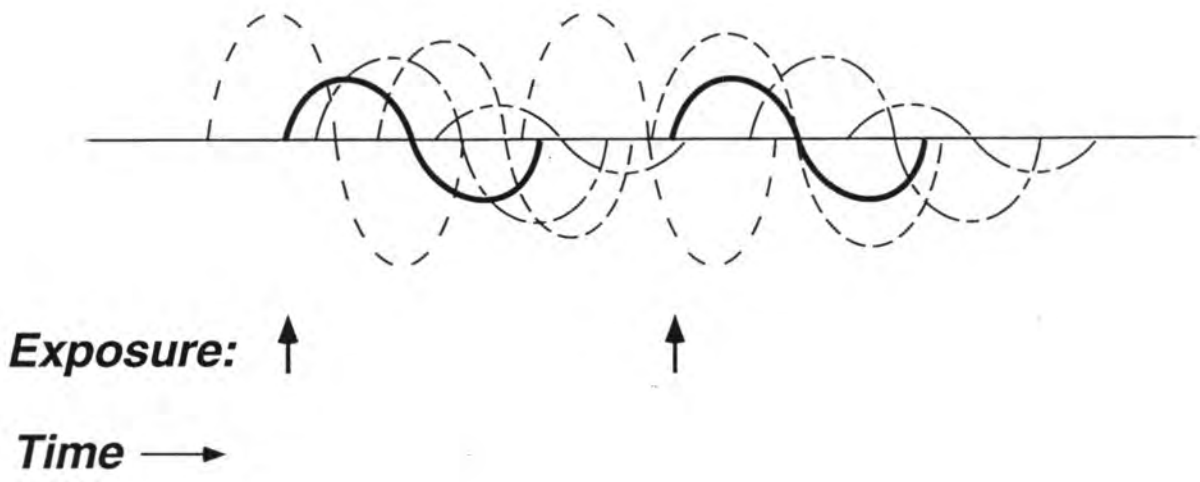


FIGURE 6. Addiction. A sensitive person who is addicted to caffeine, alcohol, nicotine, or another substance may deliberately take that substance at frequent, carefully-spaced intervals to avoid unpleasant withdrawal symptoms. Such exposures may also mask the effect of interest (e.g., a challenge test using xylene).

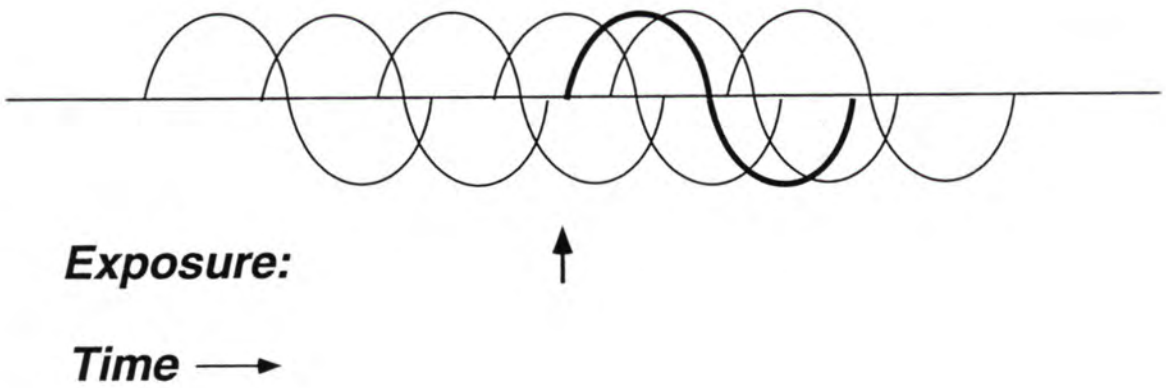


FIGURE 7. Testing Toxicant-induced Loss of Tolerance Postulates Using an Environmental Medical Unit. In the left-most portion of the figure, before entering the Environmental Medical Unit (EMU), a chemically sensitive individual is experiencing symptoms in response to multiple exposures (chemicals, foods, drugs). Effects overlap in time. The effect of any particular exposure cannot be distinguished from the effects of other exposures, and the person's symptoms may appear to wax and wane unpredictably over time.

Postulate 1.	When all chemical, food and drug incitants are avoided concurrently, remission of symptoms occurs. Anecdotally, patients report going through "withdrawal" or "detox" for the first several days and experiencing increased irritability, headaches, depression, etc. After 4 to 7 days most report feeling well and theoretically are at a clean baseline.
Postulate 2.	A specific constellation of symptoms occurs with re-introduction 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 to 7 days), produces the same symptoms.

For research purposes, challenges should be conducted in a double-blind, placebo-controlled manner.

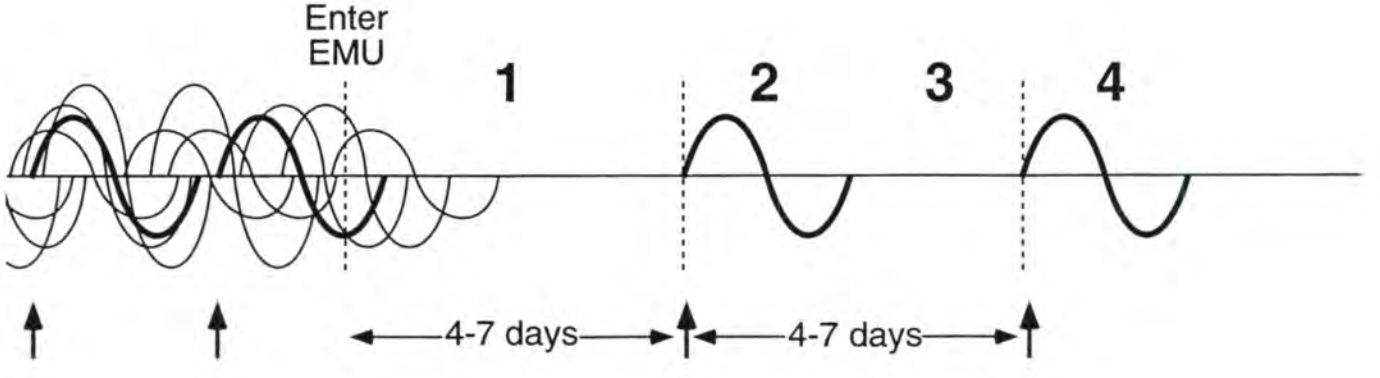
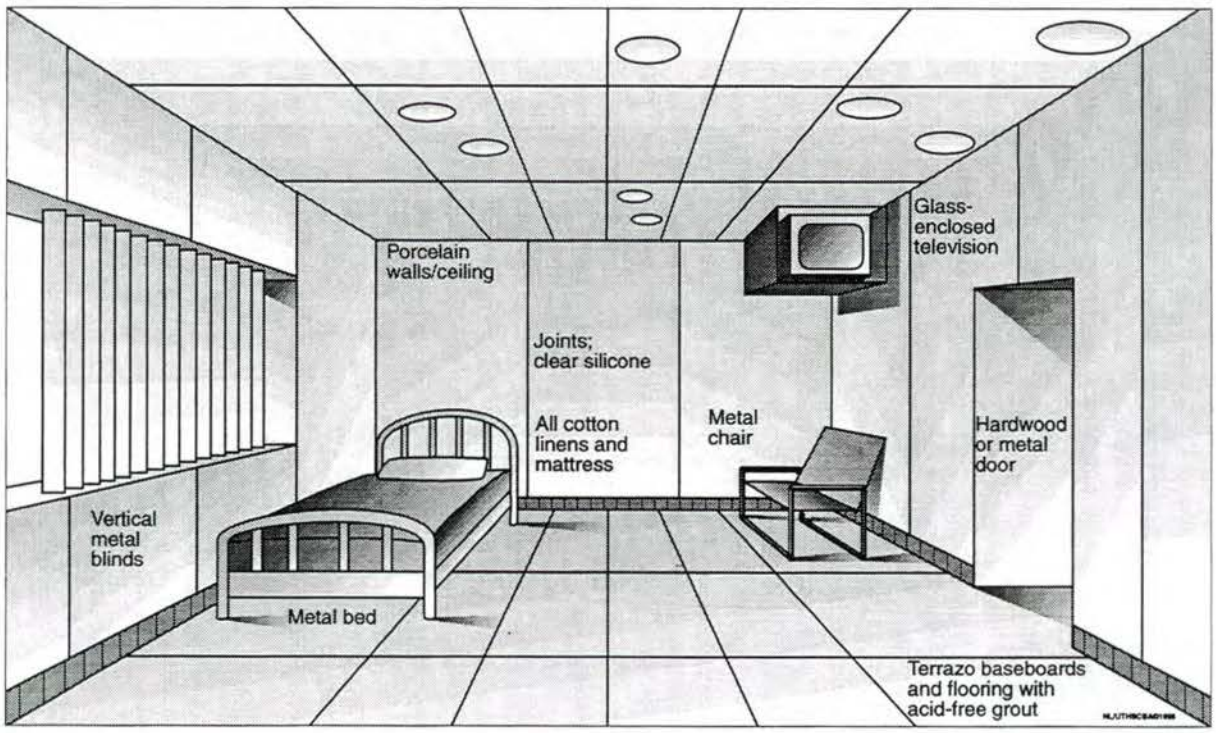


FIGURE 8. Preliminary design sketch of a patient room in an Environmental Medical Unit. Note use of non-outgassing construction materials and furnishings, and point source control (ventilated television enclosure).



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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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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.

REFERENCES

Ashford N, Heinzow B, Lütjen K, Marouli C, Molhave L, Mvönch B, Papadopoulos S, Rest K, Rosdahl D, Siskos P, Velonakis E. Chemical Sensitivity in Selected European Countries: An Exploratory Study. Ergonomia Ltd. Athens, Greece (1994).

Ashford NA, Miller CS. Chemical Sensitivity. A Report to the New Jersey State Department of Health (1989).

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

Association of Occupational and Environmental Clinics. Advancing the understanding of multiple chemical sensitivity. Toxicol Ind Health 8(4):1-257 (1992).

Cone JE, Sult TA. Acquired intolerance to solvents following pesticide/solvent exposure in a building: a new group of workers at risk for multiple chemical sensitivities? Toxicol Ind Health 8(4):29-39 (1992).

Miller CS. Chemical sensitivity: symptom, syndrome or mechanism for disease? Toxicology 111:69-86 (1996).

Miller CS. Toxicant-induced loss of tolerance: An emerging theory of disease? Environ Health Perspect (in press).

Miller CS, Mitzel HC. Chemical sensitivity attributed to pesticide exposure versus remodeling. Arch Environ Health 50(2):119-129 (1995).

National Research Council. Multiple Chemical Sensitivities: Addendum to Biologic Markers in Immunotoxicology. Washington, D.C.: National Academy Press (1992).

Rosenthal NE, Cameron CL. Exaggerated sensitivity to an organophosphate pesticide (letter). Am J Psychiatry 148(2):270 (1991).

Sherman JD. Organophosphate pesticides-neurological and respiratory toxicity. Tox Ind Health 11(1):33-38 (1995).

Spiegelberg V. Psychopathologisch-neurologische Schäden nach Einwirkung Synthetischer Gifte. In Wehrdienst und Gesundheit, Vol. III. Darmstadt: Wehr und Wissen Verlagsgesellshaft (1961).

Tabershaw IR, Cooper C. Sequelae of acute organic phosphate poisoning. J Occup Med 8:5-20 (1966).

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

Symptom Category	Number
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

	%
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

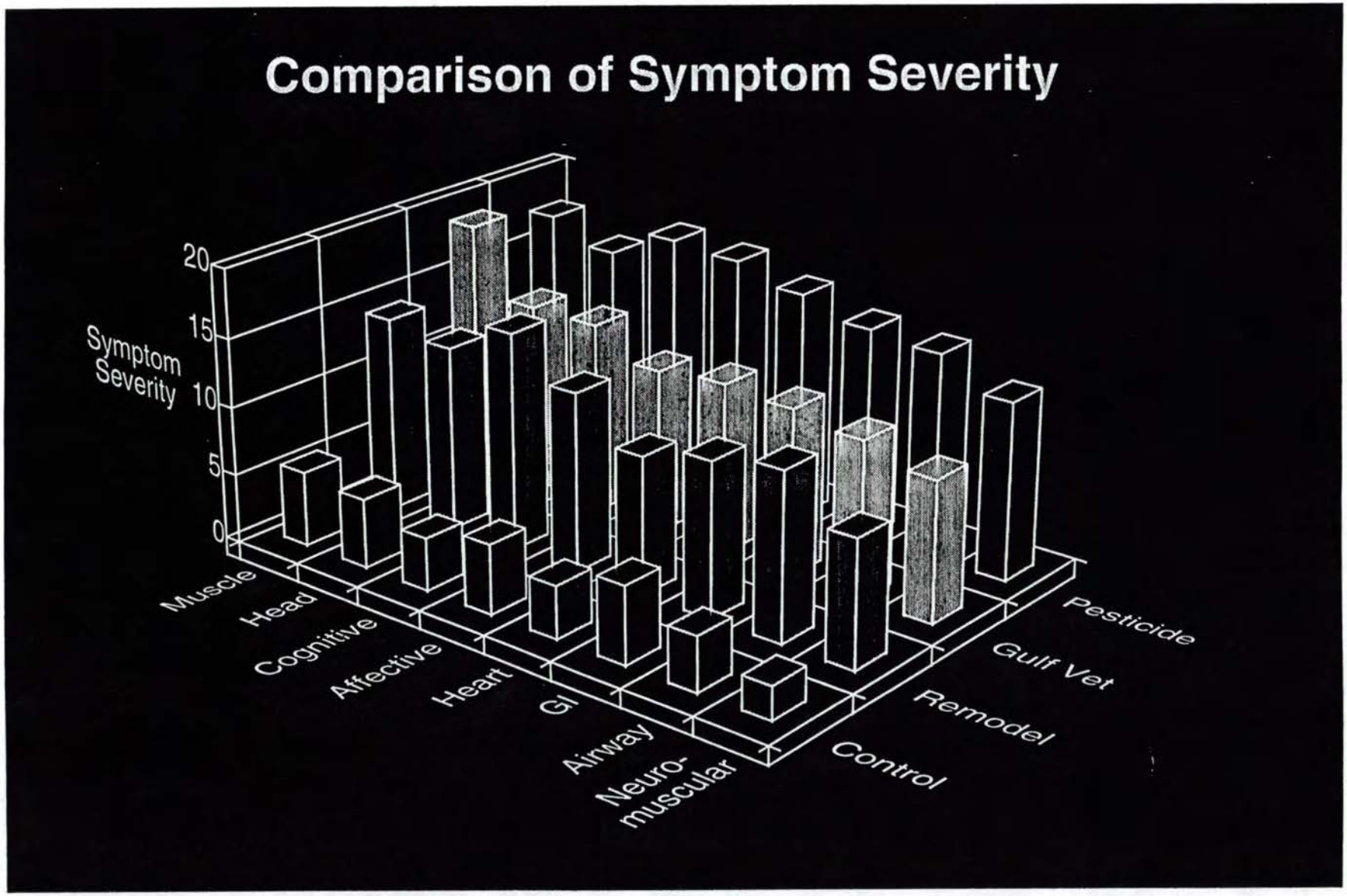

Comparison of Symptom Severity
Symptom Severity
20
15
10
5
0
Muscle
Head
Cognitive
Affective
Heart
GI
Airway
Neuro-muscular
Control
Remodel
Gulf Vet
Pesticide

Figure 1

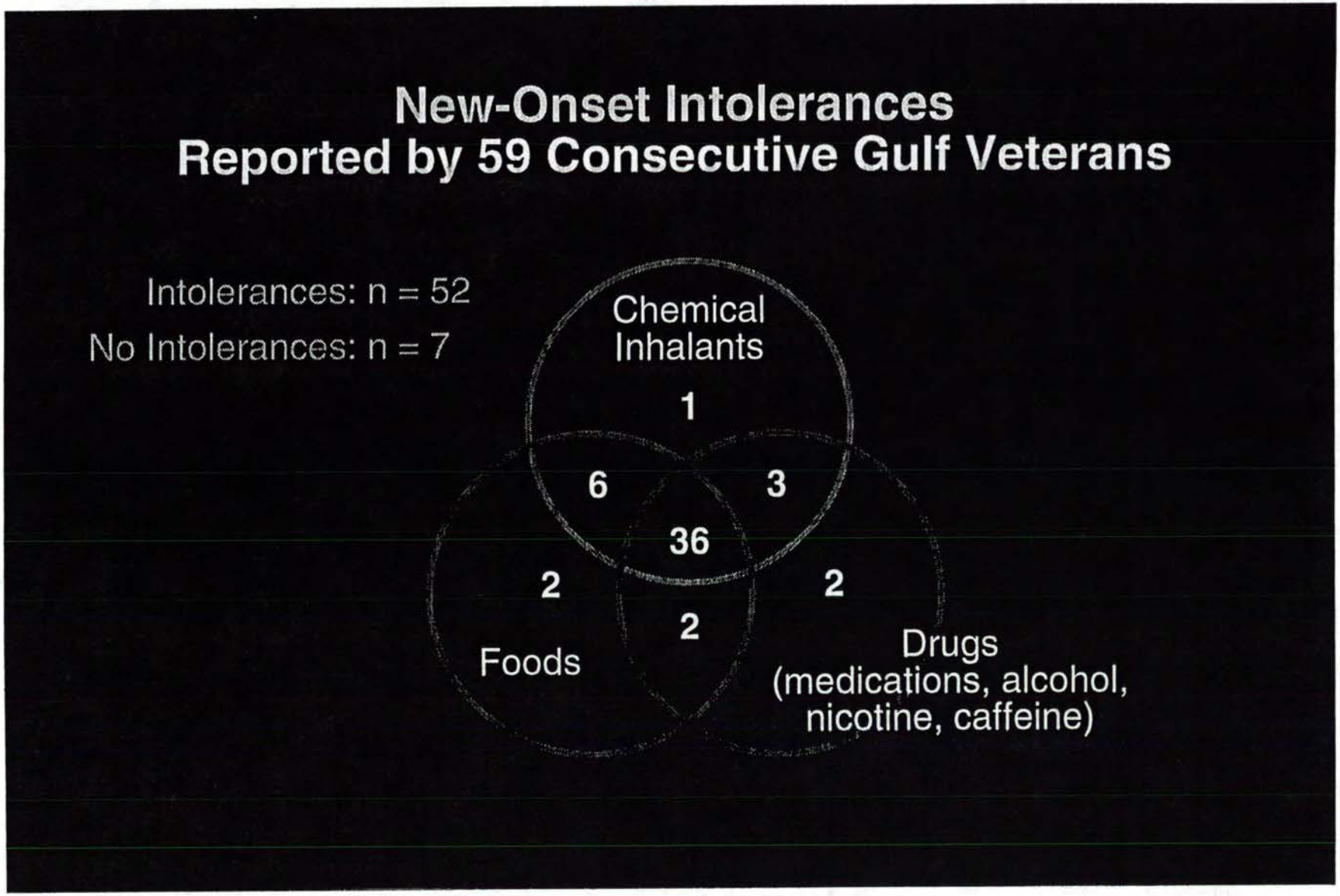
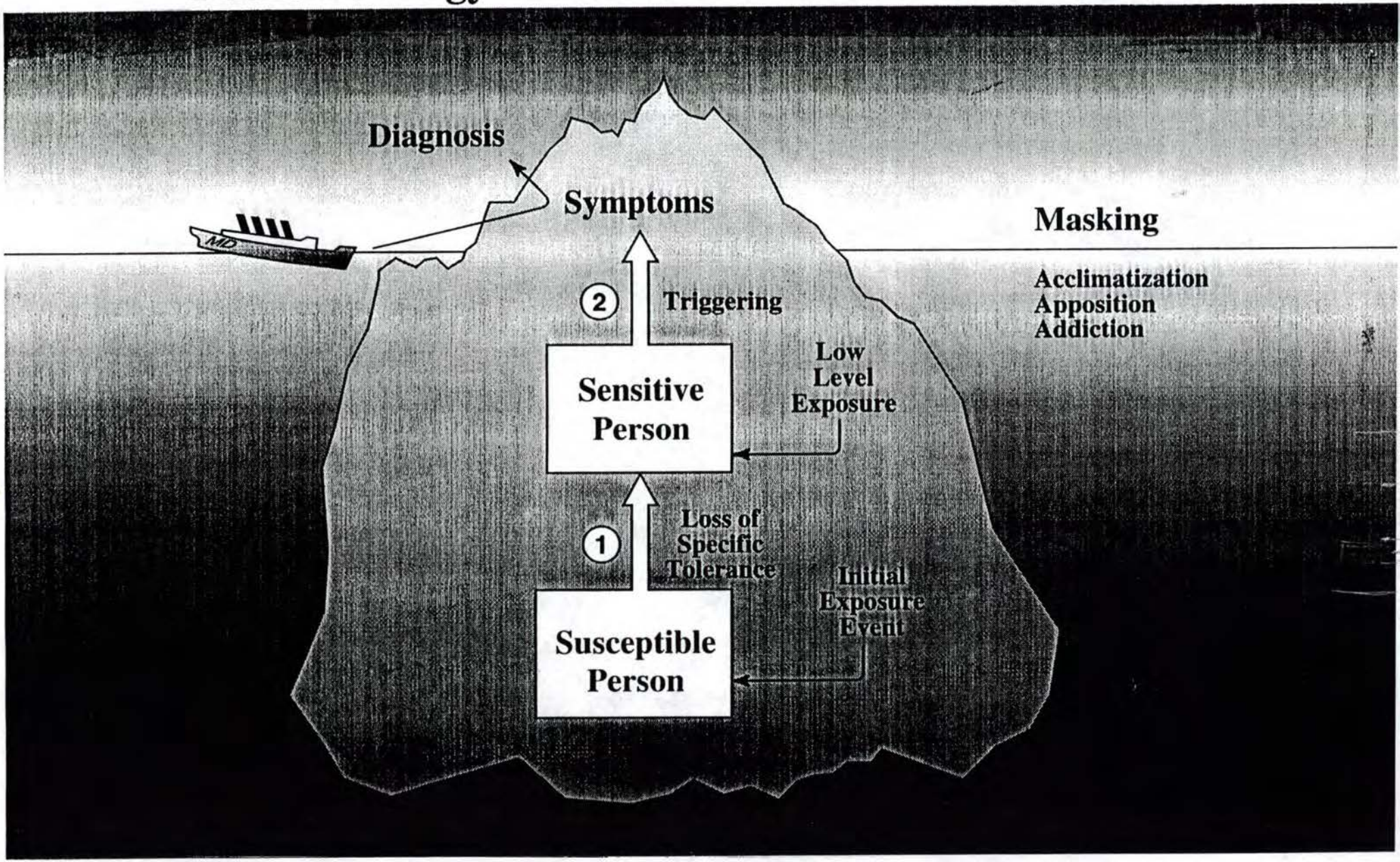

New-Onset Intolerances
Reported by 59 Consecutive Gulf Veterans
Intolerances: n = 52
No Intolerances: n = 7
Chemical Inhalants
1
6
3
36
2
2
2
Foods
Drugs
(medications, alcohol, nicotine, caffeine)

Figure 2

Phenomenology of Toxicant-induced Loss of Tolerance



Miller-402156

Figure 3

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Chemical Sensitivity Attributed to Pesticide Exposure Versus Remodeling

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HOWARD C. MITZEL
Department of Family Practice
Environmental and Occupational Medicine
The University of Texas Health Science
Center at San Antonio
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.

Presidential Advisory Committee on Gulf War Veterans' Illnesses
Meeting on February 27, 1996, in San Antonio, Texas
Invited Presentation by Claudia S. Miller, M.D., M.S.

Environmental and Occupational Medicine
University of Texas Health Science Center at San Antonio
7703 Floyd Curl Drive
San Antonio, Texas 78284-7794
(210)567-4557

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.

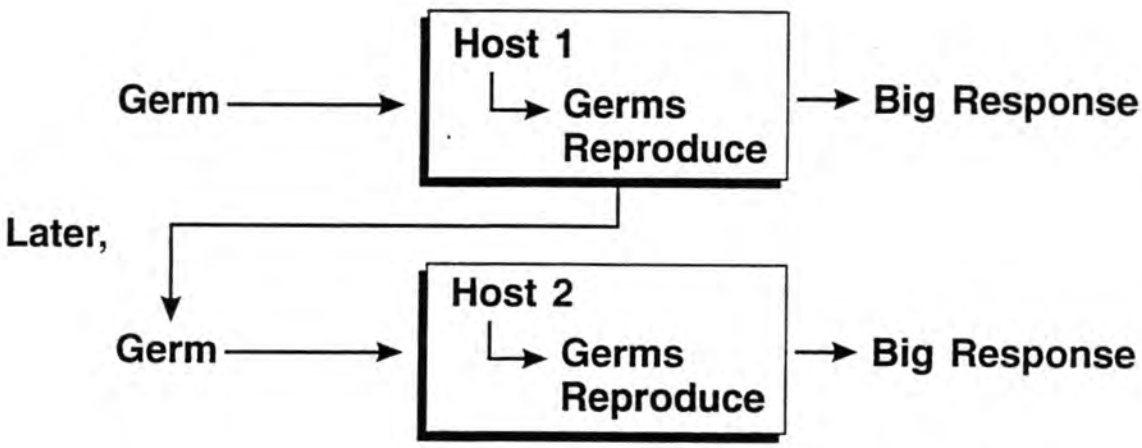
d) The observation that many MCS patients who have avoided problem chemicals and foods report marked improvement or resolution of their symptoms.

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:

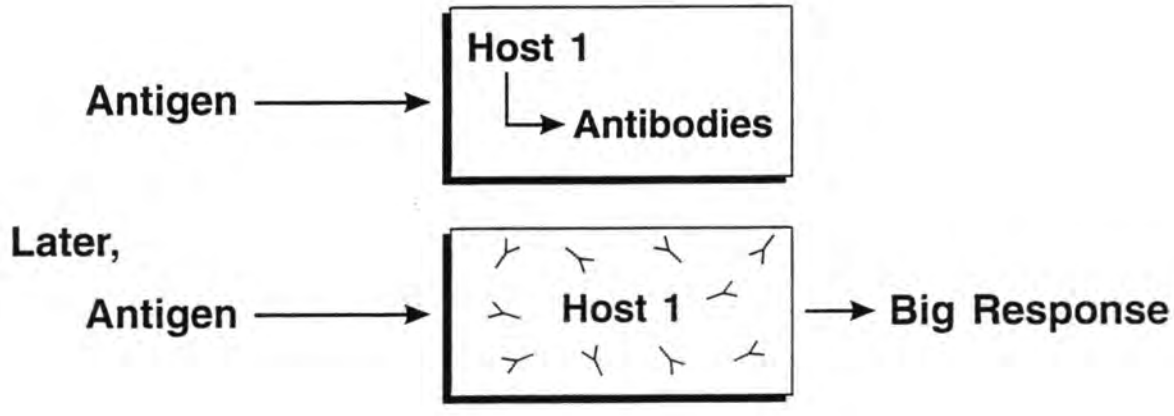


Note that:

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:



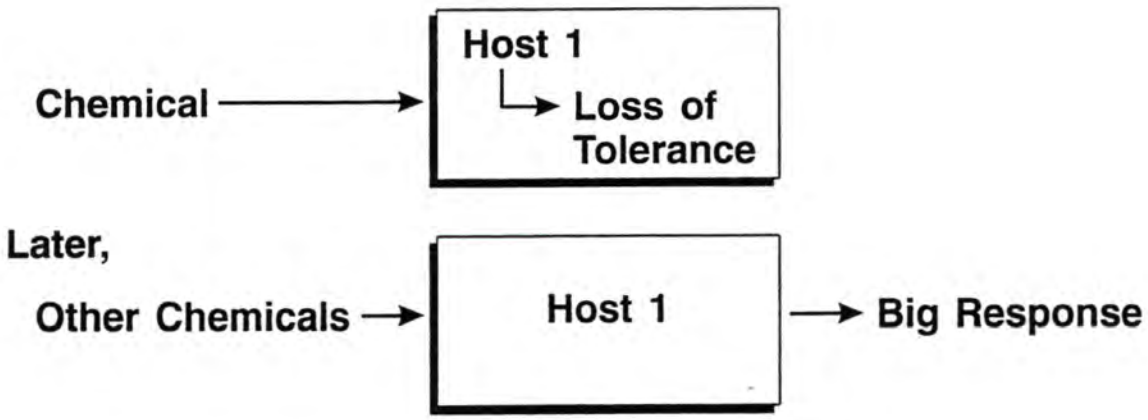
Once again, notice that:

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.

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b(9) Release would disclose geological or geophysical information concerning wells [(b)(9) of the FOIA]

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.: (b)(6) C0013

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

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) (components 1 and 2)	1988	

2. Recertification

n/a

3. Licensure

State	Date Issued	Perm/Temp	Number	Renewal Date
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

Date	Setting	Level	weeks per yr	hours per wk
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 Practioners	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 Musculosketal 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? (invied 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 Eduction 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

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, *Environmental Health Perspectives*, 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, *Inhalation Toxicology*
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, *Toxicology and Industrial Health*
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, *Aerospace Medicine and Aviation*
1994	Reviewer, *Journal of the American Medical Association*
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

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

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

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)

file Gulfwar

White House Press Release

REMARKS BY THE PRESIDENT AND THE FIRST LADY AND DR. JOYCE LASHOF ON RECEIVING THE PRESIDENTIAL ADVISORY COMMITTEE REPORT ON GULF WAR ILLNESSES

THE WHITE HOUSE

Office of the Press Secretary

For Immediate Release January 7, 1997

REMARKS BY THE PRESIDENT
AND THE FIRST LADY AND DR. JOYCE LASHOF
ON RECEIVING THE PRESIDENTIAL ADVISORY COMMITTEE REPORT
ON **GULF WAR** ILLNESSES

The Roosevelt Room

10:55 A.M. EST

MRS. CLINTON: Thank you, and please be seated and welcome to the White House. I am pleased to see all of you here today for the presentation of this report of the Presidential Advisory Committee on **Gulf War** Veterans Illnesses. The work of this committee reflects the administration's commitment to finding answers for the thousands of brave men and women suffering from undiagnosed illnesses after serving in the Persian **Gulf War**. And it reflects the President's abiding commitment to being responsive to and responsible for our veterans and their families.

I know that there are numbers who are here of the commission, and I'd like them, if they would, to stand so that we could see all -- they're all standing. (Laughter.) We appreciate very much the time and effort that went into this service. And I know firsthand how important and difficult your task has been.

Over the last four years the President and I have received many heart-wrenching letters from **Gulf War** veterans and family members. Many veterans and their family members said they felt that their country had forgotten them. So in the fall of 1994, the President asked me to explore the issues surrounding the health needs of **Gulf War**

veterans and to look into the federal government's efforts to address their concerns.

I met with officials from the Department of Defense, the Veterans Administration, and the Department of Health and Human Services to determine if we were doing the very best we could to respond to our veterans' needs and to facilitate research into their illnesses.

I met with representatives of the American Legion and the Veterans of Foreign **Wars** who shared their own observations and told me of their efforts to bring more serious national attention to these illnesses. And I visited with individual veterans, active-duty soldiers and their families. At Walter Reed Hospital and the Veterans Hospital here in Washington, I listened to veterans as they tried to describe to me what it was like to live day after day, year after year, not knowing why they had become sick. I heard stories of hard-working men and women who could no longer keep steady jobs and support their families because of their illnesses. One veteran officer who had been diagnosed as one hundred percent disabled told me about the healthy and active life he had led before his tour in the Persian **Gulf** and about his frustration in seeking effective treatments for his systems.

In February 1995, I reported to the President and the Chief of Staff on these findings and recommended some steps the administration could take in the future, including the creation of a blue ribbon panel to investigate these issues further. And I had the privilege of testifying at the first meeting of this committee in August 1995, and I've been following the work that has been done closely ever since.

So I'm particularly gratified to be here today, and I'm also gratified that our government is making progress and being responsive in taking affirmative steps to do all that can be done on behalf of our veterans and on behalf of future members of our forces who might be put in harm's way in the future.

I want to thank all who served for their persistent efforts on this committee, and for considering thoroughly the diverse and strongly held opinions, theories, explanations, and evidence about these illnesses. But I particularly want to thank **Gulf War** veterans and their families for taking the time to share their experiences with this committee. We could not have had a better chair-person of this presidential committee than the one who was persuaded to undertake this significant responsibility, and it's my pleasure now to introduce Dr. Joyce Lashof, who will tell us more about the committee's findings.

DR. LASHOF: Thank you very much, Mrs. Clinton, especially for your compassion and your interest in this important issue. And thank you, Mr. President, for your very courageous leadership for wanting to get to the bottom of this issue and the effort you've made to bring this committee about.

Mr. President, Secretary Shalala, Secretary Brown, Deputy Secretary White, and Deputy Director Tenet: On behalf of the Advisory Committee it is a pleasure for me to transmit to you this, our final report.

Over the past 16 months we have conducted a broad analysis of issues related to health consequences of **Gulf War** service. Our efforts to address the complexities of **Gulf War** veterans' illnesses would not have been possible without the contributions of hundreds of **Gulf War** veterans and their families. They have served with distinction, and we thank them.

Our interim and final reports make several recommendations which we believe can improve the government's approach to addressing the health concerns of veterans who served in the **Gulf**. In all areas save one, these suggestions are to fine-tune the government's programs on **Gulf** health matters. Overall, the government has responded with a comprehensive series of measures to resolve questions about **Gulf War** veterans' illnesses.

Unfortunately, the positive nature of these efforts has been diminished by how the Department of Defense approached the possibility that U.S. troops had been exposed to chemical weapons. It is essential now to move swiftly to resolving **Gulf War** veterans' principal remaining concern -- how many U.S. troops were exposed to chemical warfare agents and to what degree.

The committee is pained by the atmosphere of government mistrust that now surrounds every aspect of **Gulf War** veterans illnesses because of these concerns. It is regrettable, but also understandable. Our investigation of DOD's efforts related to chemical and biological weapons led us to conclude the Department's early efforts were superficial and lacked credibility. DOD's failure to seriously investigate these issues also adversely affected decisions related to funding research on health effects of low-level exposure to chemical warfare agents. DOD was intransigent originally in refusing to fund such research until late this year. This has done a disservice to the veterans and the public.

But the committee recognizes that in November 1996, DOD announced it was expanding its investigation and research related to low-level chemical warfare agent exposure. We hope these initiatives can begin to restore confidence in DOD's investigation on chemical agent incidents.

But moving beyond the specific, albeit important, topic, it is important to reiterate that many veterans clearly are experiencing health difficulties connected to their service in the **Gulf**. First and foremost, it is vital that the government continue to provide the excellent clinical care for these veterans. Next, we must try to find why they are sick. Based on existing scientific data, none of the individual environmental **Gulf War** risk factors commonly suspected appears to be the cause. And while the government finds that stress is -- while the committee finds that stress is likely to be an important contributing factor to **Gulf War** veterans illnesses, the story is by no means complete.

Veterans, their physicians, and policymakers clearly stand to benefit greatly from the comprehensive range of ongoing research. We believe a continued commitment to long-term studies is important. Some health effects such as cancer would not be expected to appear until a decade or more after the end of the **Gulf War**.

Additionally, the committee recommends new research in three areas: the long-term health effects of low-level exposure to chemical warfare agents; the synergistic effect of pyridostigmine bromide with other **Gulf War** risk factors; and the most physical response to stress.

However, veterans and their families will realize maximum benefits from such research only through a thoughtful, inclusive dialogue between veterans and the Departments. In light of current public skepticism, the committee strongly believes that a sustained risk communication effort is the only way to repair public trust.

The volunteers who served in defense of our national interest deserve complete and accurate information about the risks they

faced, and I am sure that we will be able to provide it to them.

The committee also felt there were lessons to be learned about health matters based on **Gulf War** experience. We believe the government can avoid many future post-conflict health concerns through better communication, better data, and better services, and we make recommendations in all these areas.

In closing, I would like to reemphasize that in many important and, in some places, unprecedented ways, the nation has begun to pay its debt to the 697,000 men and women who served in Operation Desert Shield-Desert Storm. We were impressed with the research the government had already initiated to understand the nature and causes of the illnesses so many veterans suffer from. The committee hopes the same degree of commitment will be applied to the issues still outstanding.

Finally, the committee gratefully acknowledges the significant time and effort that individuals within and outside government devoted to our effort. We also have been fortunate to have a talented and dedicated staff. On their behalf and on behalf of my fellow committee members, I thank you for your leadership in addressing **Gulf War** veterans' health concerns and for providing us with the unique opportunity to contribute to this vitally important issue. (Applause.)

THE PRESIDENT: Thank you very much to Dr. Lashof and the members of the Presidential Advisory Committee on **Gulf War** Illnesses. Secretary White, Secretary Brown, Secretary Shalala, Deputy Director Tenet. I'd like to say a special word of thanks to Dr. Jack Gibbons for the work that he did on this. I thank Senator Rockefeller, Senator Specter, Congressman Lane Evans for their interest and their pursuit of this issue, and all the representatives from the military and veterans organizations who are here.

I am pleased to accept this report. I thank Dr. Lashof and the committee for their extremely thorough and dedicated work for 18 months now. I pledge to you and to all the veterans of this country, we will now match your efforts with our action.

Six years ago hundreds of thousands of Americans defended our vital interest in the Persian **Gulf**. They faced a dangerous enemy, harsh conditions, lengthy isolation from their families. And they went to victory for our country with lightening speed. When they came home, for reasons that we still don't fully understand, thousands of them became **ill**. They served their country with courage and skill and strength, and they must now know that they can rely upon us. And we must not, and will not, let them down.

Three years ago I asked the Secretaries of Defense, Health and Human Services, and Veterans Affairs to form the Persian **Gulf** Veterans Coordinating Board to strengthen our efforts to care for our veterans and find the causes of their illnesses. I signed landmark legislation that pays disability benefits to **Gulf War** veterans with undiagnosed illnesses. DOD and VA established toll-free lines and medical evaluation programs.

I am especially grateful to the First Lady who took this matter to heart and first brought it to my attention quite a long while ago now. I thank her for reaching out to the veterans and for making sure that their voices would be heard.

To date, we have provided **Gulf War** veterans with more than 80,000 free medical exams. We've approved more than 26,000 disability claims. HHS, DOD and the Veterans Department have sponsored more than 70 research projects to identify the possible causes of the illnesses.

But early on, it became clear that answers were not emerging fast enough. Hillary and I shared the frustration and concerns of many veterans and their families. We realized the issues were so complex they demanded a more comprehensive effort. That is why, in May of 1995, I asked some of our nation's best doctors and scientists, as well as **Gulf War** veterans themselves, to form a presidential advisory committee that could provide an open and thorough and independent review of the government's response to veterans' health concerns and the causes of their ailments.

Since that time, we have made some real progress. The Department of Defense with the CIA launched a review of more than five million pages of **Gulf War** documents, declassifying some 23,000 pages of materials and putting them on the Internet. Through this effort, we discovered important information concerning the possible exposure of our troops to chemical agents in the wake of our destruction of an arms depot in southern Iraq.

The committee made clear, and the Defense Department agrees, that this new information demands a new approach, focusing on what happened not only during but after the **war** and what it could mean for our troops. Based on the committee's guidance, the Department of Defense has restructured and intensified its efforts, increasing tenfold its investigating teams, tracking down and talking to veterans who may have been exposed to chemical agents, and devoting millions of dollars to research on the possible effects of low-level chemical exposure.

I'm determined that this investigation will be comprehensive and credible. We haven't ended the suffering; we don't have all the answers; and I won't be satisfied until we have done everything humanly possible to find them.

That's why I welcome this committee's report and its suggestions on how to make our commitment even stronger. I also take seriously the concern regarding DOD's investigation of possible chemical exposure. I'm determined to act swiftly on these findings not only to help the veterans who are sick, but to apply the lessons of this experience to the future.

I've asked the Secretaries of Defense, Health and Human Service, and Veterans Affairs to report to me in 60 days with concrete, specific action plans for implementing these recommendations. And I am directing Secretary-designate Cohen, when confirmed by the Senate, to make this a top priority of the Defense Department.

I'm also announcing two other immediate initiatives. First, I've asked this committee to stay in business for nine more months to provide independent, expert oversight of DOD's efforts to investigate chemical exposure, and also to monitor the government-wide response to the broader recommendations. The committee's persistent public effort has helped to bring much new information to light and I have instructed them to fulfill their oversight role with the same intensity, resolve and vigor they have brought to their work so far. Dr. Lashof has agreed to continue and I trust the other committee members will as well.

Second, I'm accepting Secretary Brown's proposal to reconsider the regulation that **Gulf War** veterans with undiagnosed illnesses must prove their disabilities emerged within two years of their return in order to be eligible for benefits. Experience has shown that many disabled veterans have their claims denied because they fall outside the two-year time frame. I've asked Secretary Brown to report back to me in 60 days with a view toward extending that limit.

And we will do whatever we can and whatever it takes to research **Gulf War** illnesses as thoroughly as possible. Every credible possibility must be fully explored, including low-level chemical exposure and combat stress.

I know that Congress shares our deep concern, and let me again thank Senator Specter, Senator Rockefeller and Congressman Evans for being here. Caring for our veterans is not a partisan issue, it is a national obligation, and I thank them for the approach that they have taken.

As we continue to investigate **Gulf War** illnesses, let me again take this opportunity to urge the Congress to ratify the Chemical Weapons Convention which would make it harder for rogue states to acquire chemical weapons in the future, and protect the soldiers of the United States and our allies in the future.

This report is not the end of the road, anymore than it is the beginning. We have a lot of hard work that's been done and we have made some progress, but the task is far from over. The committee's assessment gives me confidence that we are on the right track, but we have much yet to learn and much to do.

As we do make progress, we will make our findings public. We will be open in how we view **Gulf War** illnesses and all their possible causes -- open to the veterans whose care is in our hands; open to the public looking to us for answers. I pledge to our veterans and to every American, we will not stop until we have done all we can to care for our **Gulf War** veterans, to find out why they are sick, and to help to make them healthy again.

Thank you very much. (Applause.)

Q Mr. President, this has been studied to death. Do you believe that there is a **Gulf War illness**?

THE PRESIDENT: I believe that there are a lot of veterans who got sick as a result of their service in the **Gulf**. And I believe it took experts to determine whether there is one or a deliberation of them in exactly what the cause and connection is. That has been apparent for sometime. That's why the Congress agreed to support our efforts that for the first time paid disability payments for people with undiagnosed conditions.

And -- but let me say that this -- I think that this committee has done a good job. I think -- I want to compliment the work that has been done in the last few months by John White of the Defense Department in facing up to the things which were not done before. No one has ever suggested that anybody intentionally imposed -- exposed American soldiers to these dangers, and there is nothing -- there is no reason that anyone in this government should ever do anything but just try to get to the truth and get it out and do what is right for the veterans.

And there are also -- I think we need to be a little humble about this. There are a lot of things that we still don't know. That's what Dr. Lashof said. And that's why these research projects are so very important.

And the final thing I'd like to say is we don't know all the answers here. You heard Dr. Lashof say that sometimes when people were exposed to substances that can cause cancer it may not be manifested for 10 years, which is why I want to thank Secretary Brown for urging that we stress the two-year rule. We have to -- we have to

be vigilant about this. And my successor will be working on it. We will be monitoring this for a long time to come.

But we've got a process now the American people and the veterans and their families can have confidence in. We've got the appropriate commitment of personnel and money. And more important, we've got the appropriate commitment of the heart and mind. And I'm convinced now that we will do justice to this issue and to the people that have been affected by it.

Q Thank you, Mr. President.

END 11:05 A.M. EST

To comment on this service: *feedback@www.whitehouse.gov*

NATIONAL SECURITY COUNCIL
WASHINGTON, D.C. 20504

7343

October 31, 1997

fellow Gulf war

ACTION

MEMORANDUM FOR SAMUEL R. BERGER
JOHN H. GIBBONS
THURGOOD MARSHALL, JR.
MELANNE VERVEER

FROM: PAUL E. BUSICK

SUBJECT: Rollout Plan for the Special Report of the Presidential Advisory Committee (PAC) on Gulf War Veterans' Illnesses

Tab I is the decision memorandum outlining our proposal for a Presidential radio address to receive the PAC *Special Report*, and announce major initiatives to improve health and benefits programs for both active duty personnel and veterans. It asks the President to approve two aspects of the PAC report: (1) appointment of an independent oversight group to monitor the remaining DOD investigations; and, (2) approve the VA initiative to provide independent review of the scientific findings on Gulf War illnesses, and support establishment of a permanent statutory program for Gulf War veterans.

The proposed date for the radio address is November 8, 1997. This date will allow the President to reiterate his commitment to veterans just prior to Veterans' Day, and emphasize the health care issues that concern most veterans.

Concurrences by: David Leavy; Anne Lazzatto; James Seaton; Phil Crowley; David Zavada/OMB

RECOMMENDATION

I recommend you initial the attached decision memorandum at Tab I.

Attachments
Tab I Presidential Decision Memo
Tab A VA's Draft Legislative Proposal

cc: Sylvia Matthews
Stephanie Street

THE WHITE HOUSE

WASHINGTON

ACTION

MEMORANDUM FOR THE PRESIDENT

FROM: SAMUEL R. BERGER
JOHN H. GIBBONS
THURGOOD MARSHALL, JR.
MELANNE VERVEER

SUBJECT: Rollout Plan for the Special Report of the Presidential Advisory Committee on Gulf War Veterans' Illnesses

The *Special Report* of the Presidential Advisory Committee (PAC) on Gulf War Veterans' Illnesses is due October 31, 1997. This memorandum requests a decision on continued independent oversight of DOD's remaining investigative efforts and your support of a permanent statutory program for Gulf War veterans.

Proposal

In our view, your establishment of the PAC and the prominence of the underlying issue of government credibility argue for your continued direct involvement. We have proposed a radio address on November 8th to highlight your personal commitment to Gulf War veteran's issues in which:

- You acknowledge that you have received the PAC's *Special Report*, thank the PAC for their hard work, underscore your commitment to a thorough investigation into what happened in the Gulf, and full implementation of lessons learned:

  -- You announce that you have directed DOD/VA to initiate a new, comprehensive "Force Health Protection Program" that delivers improved health care and illness prevention to our active duty troops and veterans as a major lesson learned from the Gulf War.

-- You make a commitment to enhance the government's health risk communications with military service members as well as the general public.

-- You emphasize that DOD is responsible for the investigations into chemical and biological incidents during the Gulf War, and announce appointment of an independent oversight board to focus on DOD's remaining investigations.

-- You announce $13.2 million in new funding for research into Gulf War illnesses.

-- You announce that you have instructed VA to contract with the National Academy of Sciences to provide an independent review of the scientific findings on Gulf War veterans' illnesses to ensure that our veterans receive the health care and benefits they deserve. You will also direct VA to work with Congress to codify these activities.

- You will give the agencies 45 days to present an action plan to you based on the PAC's recommendations.

RECOMMENDATIONS

That an independent advisory group be appointed to provide oversight of the remaining DOD investigations.

Approve _____

Disapprove _____

That you support the VA initiative to contract with NAS and work with Congress on a statutory program for Gulf War veterans.

Approve _____

Disapprove _____

Attachment
Tab A VA's Draft Legislative Proposal

DISCUSSION DRAFT

105th Congress

1st Session

A BILL

To provide for independent review of available scientific and medical evidence regarding associations between Gulf War service and illnesses suffered by veterans of that service, and for other purposes.

SECTION 1. SHORT TITLE

This Act may be cited as the "Persian Gulf War Veterans Act of 1997".

SEC. 2. AGREEMENT WITH THE NATIONAL ACADEMY OF SCIENCES

(a) PURPOSE.—The purpose of this section is to provide for the National Academy of Sciences, an independent nonprofit scientific organization with appropriate expertise, which is not a part of the Federal government, to review and evaluate the available scientific evidence regarding associations between illness and service in the Persian Gulf War.

(b) AGREEMENT.—The Secretary of Veterans Affairs shall seek to enter an agreement with the National Academy of Sciences for the Academy to perform the services covered by this section.

(c) REVIEW OF SCIENTIFIC EVIDENCE.—Under an agreement between the Secretary and the National Academy of Sciences, the Academy shall conduct a comprehensive review and evaluation of the available scientific and medical information regarding the health consequences of exposures to risk factors during service in the Persian Gulf War. In conducting the study under this section, the Academy will (1) review potential risk factors of military members who served in the Southwest Asia theater of operations during the Persian Gulf War and summarize the biological plausibility that those risk factors, or the synergistic effects of combinations of those risk factors, are associated with illnesses suffered by Gulf War veterans, and (2) also review and summarize the scientific and medical evidence, and assess the strength thereof, concerning the association between Gulf War service and each medical condition, to include both diagnosed and undiagnosed illnesses, suspected of being associated with such service. In conducting such reviews and providing such summaries, the Academy shall, for each medical condition so considered, assess the latency periods, if any, between exposures to the potential risk factors and the manifestation of illnesses. The potential risk factors to be reviewed shall include, but need not be limited to, depleted uranium, pesticides, insecticides, chemical and biological warfare agents,

vaccinations, pyridostigmine bromide, heat stress, solvents, paints, fuels, smoke from oil-well fires, and sand.

(d) SCIENTIFIC DETERMINATIONS CONCERNING ILLNESSES.—(1) For each medical condition reviewed, the Academy shall determine (to the extent available scientific evidence permits) whether there is scientific evidence of an association with exposure to risk factors during Gulf War service. In making these determinations the Academy will take into account the strength of scientific evidence and the appropriateness of the scientific methods used to detect the association; whether the evidence indicates the levels of exposure of the studied populations were comparable to the exposures of Gulf War veterans; whether there is an increased risk among veterans of the Gulf War; and whether there exists a plausible biological mechanism or other evidence of a causal relationship between exposure to the risk factor or factors and the medical condition.

(2) The Academy shall include in its reports under subsection (g) a full discussion of the scientific evidence and reasoning that led to its conclusions regarding risk factors and associations under this subsection.

(e) RECOMMENDATIONS FOR ADDITIONAL SCIENTIFIC STUDIES.—The Academy shall make any recommendations it has for additional scientific studies to resolve areas of continuing scientific uncertainty relating to the health consequences of Gulf War

service. In making recommendations for further studies the Academy shall consider the existing scientific information, the additional value that could result from additional studies, and the cost and feasibility of carrying out such additional studies.

(f) SUBSEQUENT REVIEWS. —An agreement under subsection (b) shall require the National Academy of Sciences—

(1) to conduct as comprehensive a review as is practicable of the evidence referred to in subsection (c) that became available since the last review of such evidence under this section; and

(2) to make its determinations and provide summaries on the basis of such review and all other reviews conducted for purposes of this section.

(g) REPORTS.—(1) The agreement between the Secretary and the National Academy of Sciences shall require the Academy to transmit to the Secretary and the Committees on Veterans' Affairs of the Senate and the House of Representatives periodic written reports regarding the Academy's activities under the agreement. Such reports will be submitted at least once every three years (as measured from the date of the first report.)

(2) The first report under this subsection shall be transmitted not later than the end of the two-year period beginning on the date of enactment of this Act. That report

shall include (A) the determinations and discussions referred to under subsection (d), and (B) any recommendations of the Academy under subsection (e).

(h) LIMITATION OF AUTHORITY.—The authority to enter into agreement under this section shall be effective for a fiscal year to the extent that appropriations are available.

(I) SUNSET.—This section shall cease to be effective 11 years after the last day of the fiscal year in which the National Academy of Sciencies enters into its agreement with the Secretary.

SEC. 3. PRESUMPTION OF SERVICE CONNECTION FOR DISEASES ASSOCIATED WITH GULF WAR SERVICE.

IN GENERAL.—(1) Chapter 11 of title 38, United States Code, is amended by adding at the end of subchapter II the following new section:

"§ 1118. Presumption of service connection for illnesses associated with service in the Gulf War

"(a)(1) For purposes of section 1110 of this title, and subject to section 1113 of this title, any illness that (A) the Secretary determines in regulations prescribed under this section warrants a presumption of service connection by reason of having an association with Gulf War service or exposure to a risk factor experienced during such service, and (B) becomes manifest within the period of time (if any) prescribed in such regulations in a veteran who, during

active military, naval, or air service, served in the Southwest Asia theater of operations during the Persian Gulf War and was exposed to a risk factor (if any) as described in such regulations, shall be considered to have been incurred in or aggravated by such service, notwithstanding that there is no record of evidence of such disease during the period of such service.

"(2) Whenever the Secretary determines that Gulf War service, or exposure to a risk factor comparable to that experienced by Gulf War veterans, is associated with the occurrence of a disease in humans, the Secretary will prescribe regulations providing a presumption of service connection for that disease. In making such determinations, the Secretary shall take into account reports received from the National Academy of Sciences under section 2 of the Persian Gulf War Veterans Act of 1997, and all other sound medical and scientific information and analyses available to the Secretary.

"(3) In evaluating medical and scientific evidence for purposes of this section, the Secretary shall consider a scientific study to be evidence for an association if it:

(A) demonstrates a positive association between the risk factor or exposure and the outcome being investigated;

(B) has statistically significant results;

(C) is capable of replication;

(D) withstands peer review; and

(E) was designed in such a way that chance, bias, and confounding can be ruled out with reasonable confidence.

It is not neccessary for this purpose that the study demonstrate a cause-and-effect relationship.

"(4) For purposes of this section, the term "veteran of the Gulf War" means a veteran who served on active duty in the Armed Forces in the Southwest Asia theater of operations during the Persian Gulf War.

"(5) (A) Not later than 90 days after the date on which the Secretary receives a report from the National Academy of Sciences under section 2 of the Persian Gulf War Veterans Act of 1997, the Secretary shall determine whether a presumption of service connection is warranted for each disease covered by the report. If the Secretary determines that such a presumption is warranted, the Secretary, not later than 90 days after making that determination, shall issue proposed regulations setting forth the Secretary's determination.

"(B) If the Secretary determines that a presumption is not warranted, the Secretary, not later than 90 days after making the determination, shall publish in the Federal Register a notice of that determination. The notice shall

include an explanation of the scientific basis for that determination. If the disease is already included in regulations providing for presumptions of service connection, the Secretary, not later than 90 days after publication of the notice of determination that the presumption is not warranted, shall issue proposed regulations removing the presumption for the disease.

"(C) Not later than 90 days after the date on which the Secretary issues any proposed regulation under this subsection, the Secretary shall issue a final regulation. Such final regulations shall be effective on the date of issuance."

(2) The table of sections at the beginning of such chapter is amended by inserting after the item relating to section 1117 the following new item:

"1118. Presumption of service connection for illnesses associated with service in the Gulf War.".

SEC. 4. CONFORMING AMENDMENTS

(1) The caption for section 1117 of title 38, United States Code, is amended to read as follows:

"§ 1117 Compensation for disabilities due to undiagnosed illnesses occurring in Persian Gulf War veterans",

and a corresponding amendment shall be made to the item relating to section 1117 in the table of sections at the beginning of chapter 11 of that title.

(2) Section 1113 of title 38, United States Code, is amended (A) by striking out "or 1117" both places it appears and inserting in lieu thereof "1117, or 1118"; and (B) by striking out "section 1112 or 1116" and inserting in lieu thereof "section 1112, 1116 or 1117".

file Gulfwar 2/2000

Gulf War Illnesses Interagency Working Group Meeting
"The Future of GWI"
February 4, 2000
2:00 - 4:00 PM
OEOB, Room 208

Opening Remarks	Hans Binnendijk
Briefing on the MVHCB	Robert Claypool
Overview of PRD-5 Recommendations	Cliff Gabriel

General Discussion of the following questions:

Considering the PAC and PRD-5 recommendations, what will be accomplished by the end of the Administration and what will remain to be done?

What type of organization do we want to leave for the next Administration?

How do we transition to the new organization over the next 11 months?

Conclusion — Hans Binnendijk

MILITARY AND VETERANS HEALTH COORDINATING BOARD

MILITARY AND VETERANS HEALTH COORDINATING BOARD

Robert G. Claypool

Executive Director

Presentation to the NSC IWG

4 Feb 2000

MVHCB Lineage

- Presidential Advisory Committee Report
  31 Dec 96
- NSTC Interagency Work Group led to PRD-5; National Obligation published
  Aug 98
- Presidential Memorandum directing MVHCB issued 11 Nov 98
- Signed MVHCB Charter completed Mar 99

MILITARY AND VETERANS HEALTH COORDINATING BOARD

MISSION

- **To ensure effective interagency coordination in the pursuit of optimum health throughout the career of our military personnel and their families and to continue this emphasis into veteran life.**

MILITARY AND VETERANS HEALTH COORDINATING BOARD

"They (the roots of the current dispute over anthrax) lie in the Defense Department's long-term loss of medical credibility with the population it serves. That's not the way it used to be."

J. Terry Scott

MILITARY AND VETERANS HEALTH COORDINATING BOARD

VISION

- **A New focus on total health awareness, beginning with military recruitment and continuing into veteran life, will document improved health and *enhance the trust that America has in our government's commitment to our most important guarantors of our freedom and our national security.***

MILITARY AND VETERANS HEALTH COORDINATING BOARD

Strategic Goals

- **Improve delivery of health care and emphasize preventive and wellness programs.**
- **Improve knowledge of health risks through interactive communication programs.**
- **Broaden concepts of relevant research and apply results to effective policy.**
- **Identify record-keeping requirements; ensure development of a GCPR and a relational data base.**
- **Serve as a successful venue for addressing issues affecting both military and veterans and domestic populations.**

MILITARY AND VETERANS HEALTH COORDINATING BOARD

MVHCB

- **Secretaries of DVA, DoD, and DHHS *<u>are</u>* the board and serve as equal co-chairs**
- **Supported by a working staff**
  - Executive director (VA)
  - Deputy/Deployment Health (USAF)
  - Public Health Officer (USA)
  - Research Officer (USN)
  - Administrative/Secretarial (HHS)
  - Analyst (part time) VA

Working Groups

- Deployment Health Working Group
  - J4MRD (RADM Dick Mayo)
- Research Working Group
  - VA Chief, Research & Development Officer (Dr. Jack Feussner)
- Health Risk Communication Working Group
  - CDR, USACHPPM (BG Lester Martinez)

MILITARY AND VETERANS HEALTH COORDINATING BOARD

Deployment Health Goals

- **Maintain a health and fit force**
- **Minimize or eliminate adverse health effects of deployment**
- **Preserve health and well-being of those who have served and their families**
- **Strengthen national strategy to protect and defend military members from WMD**
- **Ensure accuracy, timeliness, security, and retrievability of all medical records and be able to relate them to specific deployment environments**

MILITARY AND VETERANS HEALTH COORDINATING BOARD

Research Goals

- Apply epidemiological research to determine whether deployment exposures lead to post-deployment health consequences
- Balance the research agenda
- Systemically collect population health data longitudinally for military and veterans
- Collect & assess data from deployment exposures
- Provide flexible research options for novel, unanticipated situations/opportunities
- Maintain wide range of national and international collaborative relationships to enhance research efforts

MILITARY AND VETERANS HEALTH COORDINATING BOARD

National Center for Military Deployment Health Research

- IOM proposal from a Congressional tasking to VA
- Center would be placed under auspices of MVHCB
- Calls for dedication of appropriated dollars
- Broadens research agenda
- Provides for external support body of both customers and experts
- Provides for research gap analysis, accessing national data resources, and helps translate product into policy
- Enhances research flexibility by providing option of central research funding

MILITARY AND VETERANS HEALTH COORDINATING BOARD

Health Risk Communication Goals

- **Coordinate communication between departments for military members, veterans, families, deployed civilians**
- **Coordinate dissemination of information to providers**
- **Coordinate an agenda of health risk communication research and study**
- **Coordinate analysis of options to expand electronic communication with civilian health departments**
- **Coordinate analysis of options to partner with civilian officials on developing a program for them to communicate with military and veterans.**

Outreach

- MVHCB should make **information available as needed to other executive branch agencies, the Congress, medical and scientific community, and the public.**
- **Must also have effective avenues of communication with VSOs, professional societies, the media, state and community governments, and our international partners.**
- **Develop and implement a protocol and infrastructure for establishing an integrated electronic web page.**

MILITARY AND VETERANS HEALTH COORDINATING BOARD

Mission

Charter

Staff

Bios

Meeting Minutes

White House Initial Fact Sheet

PRD5

What's New

Other Links:

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Defense LINK News

Stars and Stripes

In August 1998, Neal Lane, Assistant to the President for Science and Technology, wrote "We have a national obligation to protect the health of our military, veterans, and their families. The Gulf War highlighted both our successes and failures in fulfilling that obligation. Even though the number of casualties was low, Federal agencies responsible for the health of our troops were not fully prepared to prevent or to deal with the health issues that followed the war. We must do better..."

The Military and Veterans Health Coordinating Board was established to meet this goal, as a result of National Science and Technology Council Presidential Review Directive 5.

"Mission, Objectives and Scope of Activities:

The primary mission of the Board is to ensure coordination among the Departments of Veterans Affairs, Defense, and Health and Human Services on a Broad range of military and veterans health matters to achieve the Nation's commitment to maintain, protect, and preserve the health of the men and women who serve in the U.S. Armed Forces. The Board addresses health matters that relate to military service with a primary focus on the health of military members, veterans, deployed civilians, and their families during and after future combat and other operations.

The board addresses health matters related to current and past members of the Active and Reserve Components (including the National Guard) of the U.S. Armed Forces. The responsibilities of the Board include coordination of those responsibilities and activities that are statutorily prescribed for the participating agencies. The Board provides recommendations and coordination for the deployment health and research activities as well as for outreach and health risk communication efforts with veterans, the public, and other federal government entities,

military and veterans' service organization, health professionals, scientific professional societies, the media, and state, county, and local governments."

For assistance contact: Web Administrator MVHCB

Last Updated: 02.02.00

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Challenges

- Triumvirates are tricky.
- But, commitment leads to results.
  - **(The whole is greater than the sum of the parts)**
- Old models for health, research, and communication need overhaul.
- Money, people, space.
  - 5.4 people to do the work.
  - Housekeeping budget only
  - Space…the last frontier!

MILITARY AND VETERANS HEALTH COORDINATING BOARD

Challenges (cont)

- Maintain faith with the Persian Gulf Veterans while their health interests become subsumed in the broader MVHCB agenda
- Legislative issues revolving around Public Law 102-585 and 105-368

VA Sec. Research reports to Congress Research Advisory Comm.

- Assure VSOs they will be represented on a MHVCB advisory body. Communicate with Congress.

Requirements

- Public affairs: respond to outside inquiries, draft and coordinate news releases
- VSO Liaison: establish and maintain close communication.
- Writer/editor/tech watch
- Web Master
- Risk communication staff officer
- Evaluate need for safety/industrial hygiene

Resourcing Options

- Contract for the appropriate number of FTEs
- Detail/transfer federal military or civilian personnel

MILITARY AND VETERANS HEALTH COORDINATING BOARD

"Those who ignore history are destined to repeat it."

Arnold Toynbee

File: Gulfwar

NATIONAL SECURITY COUNCIL

FAX COVER SHEET

NATIONAL SECURITY COUNCIL

17th & Penn, N.W.
Washington, D.C.
20504

Did you get a complete, clear transmission? If not, please call:

(202) 456-9191

or reach Julie Mitchell at (202) 456-9185

From: Dr. Hans Binnendijk

To: Senator Warrren Rudman PSOB

Honorable Jesse Brown (703-696-4062)

Dr. Bernard Rostker OSAGWI (703-693-1992)

J. Jarrett Clinton DOD (703-697-4197)

RADM Richard Mayo JCS (703-697-0510)

ADM David Satcher HHS

Dr. Peter Mazzella (202-260-7425)

Dr. Robert Claypool MVHCB

COL Craig Postlewaite (202-273-9912)

Tom Garthwaite VA

Dr. Fran Murphy

Dr. John Fuessner, FAX-202-273-8284)

Dr. Susan Mather

Kelley Brix

Dr. Mark Brown (202-273-9080)

Ms Melanne Verveer (x66244)

Dr Cliff Gabriel OSTP (x66027)

Sean O'Shea Cabinet Affairs (x62572)

Message: Here is the Agenda for the GWI IWG that will be held August 30, 2000 from 3:30-5:00PM in Room 208 of the Old Executive Office Building. If you have not already done so, please call Julie Mitchell (202-456-9185) and relay your name, birth date, and social security information so that you can gain entry into the building.

Please call Randy Beardsworth with questions 202-456-9188.

Thank You.

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Gulf War Illnesses Interagency Working Group Meeting
August 30, 2000
3:30 - 5:00 PM
OEOB Room 208

Opening Remarks	Hans Binnendijk
Update on the MVCHB	Robert Claypool
Update on OSAGWIMRMD Transition	Bernie Rostker
Khamisiyah Report and Schedule to mail letters	Bernie Rostker
Summary Documents Discussion	Hans Binnendijk

Meeting Objectives:

- Update the Interagency Group on MVCHB and OSAGWIMRMD.
- Develop/approve a concrete schedule for distributing Khamisiyah letters.
- Develop common understanding of summary document responsibilities.
- Set time frame for final meeting of the Working Group.

Conclusion — Hans Binnendijk

* Lessons re this process:
need to better response mech. + Coordination.
need to complete Khamisiyah analysis + create a way to deal with
→ unexplained illness now that there's no crisis.
preservation of records

Kamisebach -

dtb to vets re: impact to
→ those exposed & not.
max plume figures.
no correlation to hosp, Rx or disease
pattern.

ltr: may have been exposed - no evidence of
cause & a chemical prob.
less than those modeled in 97

go with ltr + other info available.
news conf'ce

MILITARY AND VETERANS HEALTH COORDINATING BOARD *

Coordinating Board

MVHCB UPDATE

Interagency Working Group (IWG) Meeting
30 August 2000

Here: met & agreed to be following.

Col R. Craig Postlewaite
MVHCB Staff Director/
Director for Deployment Health

MILITARY AND VETERANS HEALTH COORDINATING BOARD

VA DOD HHS

Briefing Topics

- PGVCB Transition to the MVHCB
- Principal Alternates' Meeting
- Plenary
- Strategic Plan Development
- Charter Renewal
- Other Issues/Activities

MILITARY AND VETERANS HEALTH COORDINATING BOARD

PGVCB Expansion Into the MVHCB

- Completed Concept Coordination: VSOs, Congressional Committees
- Joint Draft Press Release/Q's and A's being coordinated with VA, HHS and DoD
- NSC concurrence
- Info copy to VSOs
- Select date and release

MILITARY AND VETERANS HEALTH COORDINATING BOARD

Principal Alternates' Meeting

- Agenda coordinated and request for time availability sent on 14 Aug 00
- Agenda items
  - Charter revision, Strategic Plan, Advisory Committee, PGVCB Expansion into the MVHCB, IOM Proposal for Nat'l Center for Deployment Health Research

MILITARY AND VETERANS HEALTH COORDINATING BOARD

MVHCB Plenary

- Sept 12-13, Andrews AFB, ANG Readiness Center
- Dr Rostker/Dr Murphy to provide opening remarks
- Purpose: for MVHCB Working Groups as an aid in development of Working Group plans and MVHCB strategic plan
- Plan: Status of initiatives supporting approx 25 PRD-5 strategies to be briefed

MILITARY AND VETERANS HEALTH COORDINATING BOARD

MVHCB Strategic Plan

- MVHCB Charter requires Executive Director to develop an annual strategic plan for member approval
- Plan currently under review by Working Groups to be finalized as draft after plenary session.
- Projected completion date of plan: 15 Nov 00
- Will be included in annual report required by Presidential Directive to the President's Assistants for National Security Affairs and Science and Technology

MVHCB Charter Renewal

- MVHCB Charter expires 31 Dec 00, subject to rechartering
  - Original signed by SECDEF, SEC VA, SEC HHS between 12/98 and 3/99
- Redrafting of the charter has been initiated with input from the MVHCB Working Group Chairs

Other MVHCB Issues/Activities

- Move to new office space - Va
- AMSUS participation
- Personnel
  - Arrival of Navy research staff officer in Oct
  - Update of HHS Risk Communication technical specialist.
  - Organizational Charts

MILITARY AND VETERANS HEALTH COORDINATING BOARD

Military and Veterans Health Coordinating Board
Secretaries of DoD, VA, HHS

MVHCB Executive Directorate
Executive Director and Staff
Working Group and Core Activity Support

PLANNED
MVHCB Advisory Committee

MVHCB Working Group Steering Committee
MVHCB Exec Dir; DDMR, J-4; CDR CHPPM; VA CRADO, HHS OMVL

Information Management/ Information Technology Task Force

Research Working Group
Chair: VA CRADO
Dr Jack Feussner

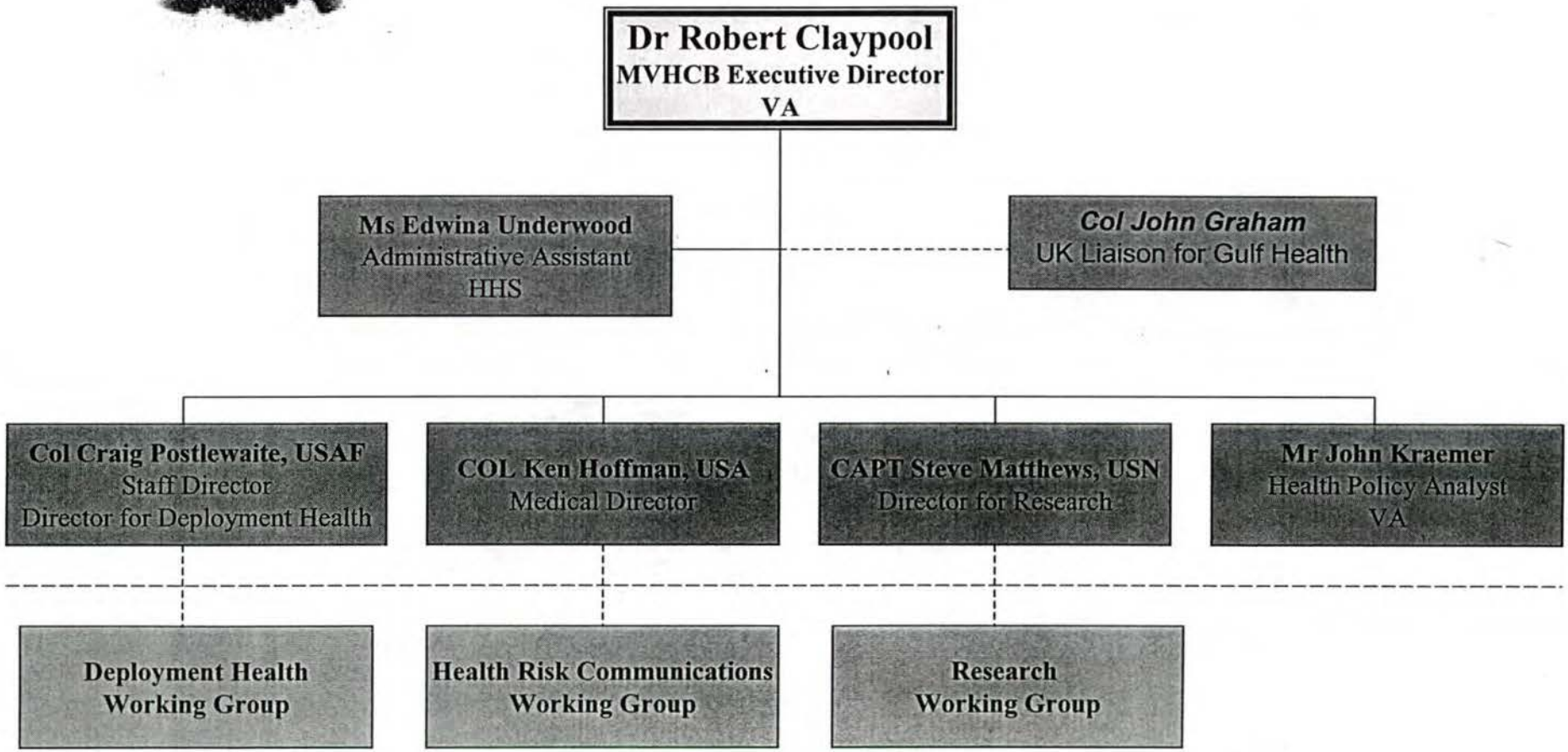
Deployment Health Working Group
Chair: J-4, MRD
RADM Richard Mayo

Health Risk Communications Working Group
Chair: CDR USACHPPM
BG Lester Martinez-Lopez

MILITARY AND VETERANS HEALTH COORDINATING BOARD

VA DOD HHS

Executive Directorate



Others Planned: Health Risk Communication Specialist (HHS)
Reservist (DoD)

Questions?

Gulf War Illnesses Summary Document Proposal
August 30, 2000

- The Gulf War Illnesses Summary Document will capture the results of our collective efforts to understand Gulf War Illness, to investigate potential causes, to treat and appropriately compensate our veterans, and to apply what we have learned from this experience to future deployments

- The document will be:
  - ***Substantive.*** Not just "bureaucracy speak." what do we know and what do we not know.
  - ***Comprehensive.*** The report should cover the efforts over the entire administration.
  - ***Professional and Readable.***
  - ***About 30 pages.***

- The document should include at least the following:
  - ***Results of Reasearch.***
  - ***Results of Investigations.***
  - ***Results of Clinical Assessments.***
  - ***Outreach programs.***
  - ***Disability and compensation.***
  - ***Lessons Learned and what we are doing as a result.***

- The Military and Veterans Health Coordinating Board Executive Director is tasked with coordinating the drafting and publication of this document. OSAGWIMRMD will provide a professional writer and additional financial resources.

- Agencies will provide assistance to MVHCB in the form of written drafts covering their area of expertise and responsibility as follows:
  - OSAGWIMRMD (Dr Rostker) – input on the roles and contributions of OSAGWI relating to investigations, outreach, lessons learned, and how we are applying those lessons for future deployments.
  - DoD HA Clinical Programs and Policy (Dr Mazzuchi) - input on clinical assessment and treatment to include contributions of the PGVCB Clinical Working Group. It will address DoD's and VA's clinical assessment program as well as lessons learned.
  - VA Chief Research and Development Officer (Dr Feussner, Chair PGVCB Research Working Group) - a summary of the research under the oversight of the PGVCB RWG including current state of knowledge regarding possible exposure agents and stresses hypothesized to have contributed to GW Illnesses as well as a summary of the on-going research effort
  - VA (Dr Garthwaite) - input on the VA's outreach effort, the compensation and benefits relating to GW illness (PGVCB Disability and Benefits Working Group), and lessons learned.

- PSOB (Mr Kaplan) - a summary of its history, roles and contributions
- MVHCB (Dr Claypool) – summary of the contributions/ activities of the PAC as well as the future contributions of the MVHCB (an outgrowth of lessons learned.)
- HHS (Peter Mazella) - summary of lessons learned as well as any additional contributions of HHS not covered in the Research piece addressed by Dr Feussner (VA)

- MVHCB will develop a timeline. We anticipate publication by December, which means a coordinated final draft has to be completed by the end of October.