



A controlled comparison of symptoms and chemical intolerances reported by Gulf War veterans, implant recipients and persons with multiple chemical sensitivity

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Using the Environmental Exposure and Sensitivity Inventory (EESI), a standardized instrument for measuring chemical sensitivity, we obtained and compared ratings of symptoms, chemical (inhalant) intolerances, other intolerances (e.g., drugs, caffeine, alcohol, skin contactants), life impact, and masking (ongoing exposures) in five populations: multiple chemical sensitivity (MCS) patients who did ($n=96$) or did not ($n=90$) attribute onset of their illness to a specific exposure event, patients with implanted devices ($n=87$), Gulf War veterans ($n=72$), and controls ($n=76$). For each patient group, mean scores on the first four scales were significantly greater than for controls. MCS patients reported avoiding more chemical exposures (were less masked) than the other groups. Across groups, for a given level of symptoms, as masking increased, mean scores on the Chemical Intolerance Scale decreased. In contrast, mean scores on the Other Intolerance Scale appeared to be less affected by masking. These findings suggest that some patients with antecedent chemical exposures, whether exogenous (chemical spill, pesticide application, indoor air contaminants) or endogenous (implant), develop new chemical, food, and drug intolerances. Reports of new caffeine, alcohol, medication, food, or other intolerances by patients may signal exposure-related illness. Masking may reduce individuals' awareness of chemical intolerances, and, to a lesser degree, other intolerances.

Keywords: *chemical sensitivity, environmental exposures, environmental illness, Gulf War veterans, implant, multiple chemical sensitivity, pesticide.*

Introduction

The first case involving a patient with multiple, disabling chemical intolerances was described nearly a half century ago (summarized in Randolph, 1987). Originally called 'the petrochemical problem,' this condition has been the subject of several federally sponsored meetings and professional conferences over the past 10 years (Ashford and Miller, 1998). Chemical intolerance or chemical sensitivity poses major scientific and policy challenges for physicians, toxicologists, employers, building owners, chemical producers, and government officials. Investigators in more than a dozen countries have reported cases arising in diverse demographic groups following exposure to indoor air

contaminants, chemical spills, industrial chemicals, and pesticides (Ashford and Miller, 1998; Ashford et al., 1995). Despite the increasing frequency of these reports in recent years, reliable comparisons as to the prevalence and degree of chemical sensitivity in various patient populations, communities, and countries are lacking. In part, this is due to the bewildering array of approaches investigators use to assess chemical sensitivity.

Between 15 and 36% of the U.S. population report being 'especially' or 'unusually' sensitive to certain chemicals, while 4–6% report physician-diagnosed multiple chemical sensitivity (MCS), environmental illness, or significant functional impairment attributed to chemical sensitivity (EPA, 1989; Bell et al., 1996; Kruezer and Neutra, 1996; Meggs et al., 1996). However, because of variations in the wording of questions and the ambiguity inherent in general survey items, uncertainty remains as to the frequency and degree of chemical sensitivity in the general population.

A recently developed, self-administered instrument, the Environmental Exposure and Sensitivity Inventory (EESI), as well as a condensed 50-item version (the Quick Environmental Exposure and Sensitivity Inventory or QEESI), were designed to assist researchers and clinicians in evaluating patients and populations for chemical

1. Abbreviations: EESI, Environmental Exposure and Sensitivity Inventory; MCS, multiple chemical sensitivity; TILT, toxicant-induced loss of tolerance.

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sensitivity.¹ Both instruments contain four core scales: Symptom Severity, Chemical (Inhalant) Intolerance, Other Intolerance, and Life Impact. In addition, both include a fifth scale, a Masking Index, designed to assess the degree of ongoing exposures individuals may have. The Symptom Severity, Chemical Intolerance, Other Intolerance, and Life Impact Scales of the EESI and QEESI have been shown to be highly reliable and exhibit good validity in that they correlate with standard survey measures of health status and life function (Miller and Prihoda, 1999). They also discriminated between chemically sensitive persons and unselected controls with good sensitivity (92%) and specificity (95%) (Miller and Prihoda, 1999).

The purpose of this study was to test the utility of these scales by comparing responses on the EESI in five groups: MCS patients (1) who did or (2) did not attribute onset of their illness to a specific exposure event, (3) patients with surgically implanted devices, (4) Gulf War veterans, and (5) controls.

Methods

Study Population

Patients were recruited via advertisements in patient group newsletters and by word-of-mouth. Announcements stated that the purpose of the study was to compare health problems and intolerances reported by MCS patients, persons with implanted devices of any type, and Gulf War veterans. It was clearly indicated that participants did not need to be sick in order to enroll in the study. Respondents were sent one copy of the questionnaire and asked to return it in a pre-paid envelope. Controls were attendees at two professional conferences, one for women leaders in Texas and the other for persons who investigate pesticide incidents in the Midwestern United States.

Instrument

Four parallel versions of the EESI were employed. Each contained identical questions and scales, except as noted below. The 'General' version, administered to controls and to MCS patients who did not identify a specific initiating event, asked respondents to rate their current symptoms, chemical intolerances, other intolerances, and the impact of their sensitivities on activities of daily living. A parallel but somewhat longer version of the same questionnaire was sent to MCS patients who attributed onset of their illness to a particular event such as a chemical spill or pesticide

exposure. This 'Exposure Event' questionnaire, as well as separate 'Implant' and 'Gulf War Veteran' versions of the EESI, had items and a format identical to those of the General version, but additionally asked respondents to rate the severity of symptoms, intolerances, and life impact of sensitivities both *before* and *since* the exposure, implants, or the Gulf War, respectively. These parallel forms of the EESI also contained additional specific questions concerning the nature of the exposures respondents felt had made them ill, e.g., type of implant and whether the implant had been removed, and exposures and symptoms the veterans may have experienced while in the Gulf.

Each of the first four scales on the EESI (listed below) contains ten items. Next to each item is a 0 to 10 rating scale. Participants are instructed to circle the number (0–10) that best corresponds with the severity of their symptoms, their responses to various substances, and the impact of their sensitivities on specific life activities: 0=not at all a problem, 5=moderate, 10=severe or disabling. Scores on the ten items for each scale are tallied to obtain a total scale score (0–100) (see Miller and Prihoda, 1999, for details of scale development).

Symptom Severity Scale The ten items on this scale were derived via factor analysis of responses to 114 symptom items previously used in a study of 112 MCS patients who attributed their symptoms to a well-defined exposure to either pesticides or indoor air contaminants (Miller and Mitzel, 1995). Items include head-related (e.g., headaches), cognitive, affective, neuromuscular, musculoskeletal, gastrointestinal, heart-related, airway/mucous membrane, skin, and genitourinary symptoms.

Chemical (Inhalant) Intolerance Scale This scale comprises ten common chemical inhalants that represent structurally diverse classes of chemicals to which MCS patients frequently attribute symptoms (Miller and Mitzel, 1995): paint or paint thinner (solvents); insecticide (pesticides); perfume (fragrances); gasoline vapors (fuels); tobacco smoke (combustion products); diesel or gas engine exhaust (petrochemical combustion products); fresh tar or asphalt (polynuclear aromatics); cleaning products such as disinfectants or bleach (structurally diverse cleaning agents); nailpolish, nailpolish remover, or hairspray (fragrances/solvents); and new furnishings such as new carpeting, a new soft plastic shower curtain, or the interior of a new car (solvents, plasticizers, formaldehyde).

Other Intolerance Scale This scale contains ten additional exposures (other than chemical inhalants) to which MCS patients frequently ascribe symptoms. These include: chlorinated tap water, foods or food additives, caffeine, alcoholic beverages, skin contactants, medical drugs and

¹ The 50-item QEESI has been published and appears in Miller and Prihoda (1999). 'The Environmental Exposure and Sensitivity Inventory (EESI): a standardized approach for measuring chemical intolerances for research and clinical applications.' *Toxicology and Industrial Health* 15(3):370–385.

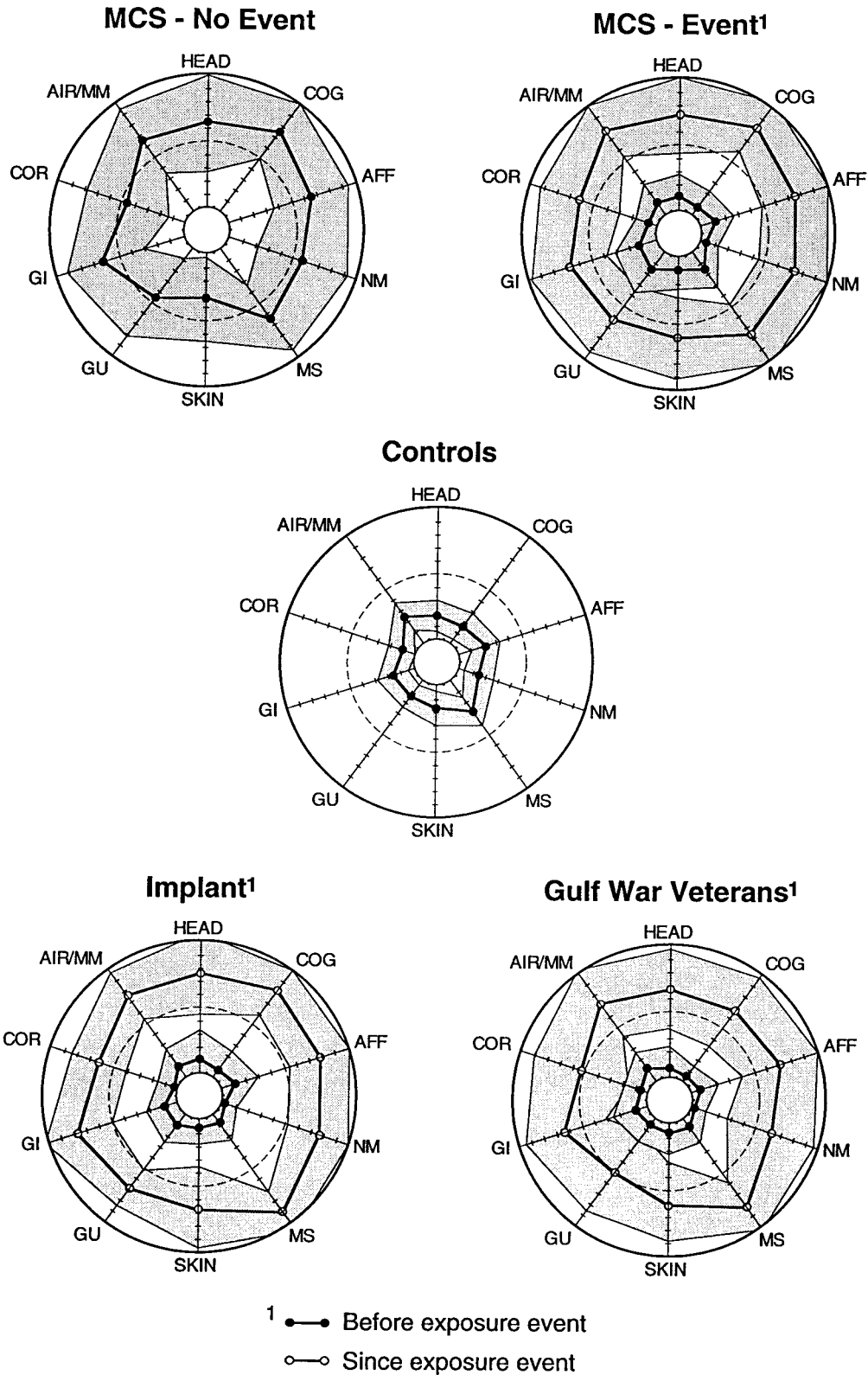


Figure 1. Mean scores on symptom items for each group plotted on the QEEESI target diagram. Shaded areas depict ± 1 standard deviation for each symptom measured. HEAD= head-related symptoms, COG= cognitive symptoms, AFF= affective symptoms, NM= neuromuscular symptoms, MS= musculoskeletal symptoms, SKIN= skin-related symptoms, GU= genitourinary symptoms, GI= gastrointestinal symptoms, COR= heart/chest-related symptoms, AIR/MM= airway or mucous membrane-related symptoms.



devices, and allergens (causing classical allergic responses of asthma, nasal symptoms, hives, eczema, or anaphylaxis).

Life Impact Scale Respondents rate the degree to which chemical or food sensitivities adversely impact each of ten aspects of their lives: diet, ability to work or attend school, choice of home furnishings, choice of clothing, ability to travel or drive, selection of personal care products (make-up, deodorant), social activities, choice of hobbies or recreation, relationship with spouse or family, and ability to perform household chores.

Masking Index The EESI and QEESI also contain ten 'masking' items. One theory about chemical sensitivity is that frequent, low level exposures to chemicals and the regular use of medications, caffeine, alcohol, and nicotine create background symptom 'noise' that reduces individuals' awareness of specific intolerances (Miller, 1997; Ashford and Miller, 1998). For each item on the EESI masking scale, respondents are directed to circle 'yes' or 'no' whether they currently have or recently have had that exposure. 'Yes' answers are scored '1' and 'no' answers as '0.' The number of 'yes' responses is tallied to arrive at a total score (0–10). A high score indicates high masking/low avoidance; a low score indicates low masking/high avoidance.

The ten masking questions ask subjects whether they regularly (once a week or more often) use tobacco products, alcoholic beverages, caffeine, certain drugs, or scented personal care products (fragrances, hairspray); whether they are exposed to chemicals at work; whether they live with a smoker; whether propane or gas fuel is used for cooking; whether pesticides have been applied in their home or workplace in the past year; and whether scented fabric softeners are used in laundering their clothes or bedding.

Data Analysis

Group means and standard errors for all scales and items on each scale were computed and compared using one-way

analysis of variance followed by comparisons of each group with the control group using the pooled variance. For categorical variables such as gender and employment status, group percentages were computed and compared with the Chi-square contingency table test. Specific significance levels are reported for each comparison done. Mean scores for individual symptom items were plotted on a symptom target diagram to allow visual comparison of group responses (Figure 1).

To explore the effect of masking on subjects' awareness of chemical intolerances and other intolerances, we used two-way analysis of variance. One factor was masking level where we divided all subjects nearly equally into low, medium, and high levels of masking. The other factor was symptoms where we divided all subjects nearly equally into low, medium, and high levels of symptoms. This provided a 3×3 factorial analysis of variance for chemical intolerance and for other intolerances. The effect of masking on the two intolerance scales could then be seen, while controlling for level of symptoms.

Results

Demographics

Sixty-one percent of the MCS patients who identified a specific initiating event (MCS-event), and 54% of MCS patients who did not (MCS-no event), 72% of implant patients, and 64% of Gulf War veterans returned questionnaires following the one-time mailing. Altogether, 421 individuals responded and were included as subjects: 96 MCS patients with, and 90 without, an initiating event; 87 implant recipients; 72 Gulf War veterans; and 76 controls. Demographics for each group are summarized in Table 1. There were no significant differences in the ages of the patient groups as compared to controls. The MCS groups and implant group, comprised primarily of patients with breast implants, had significantly more females and the Gulf War veteran group had significantly fewer females as compared to controls.

Table 1. Demographic characteristics of subjects.

	Controls (n=76)	MCS-no event (n=90)	MCS-event (n=96)	Implant (n=87)	Gulf War veterans (n=72)
Age in years, mean (SE)	43 (9)	51 (12)	49 (11)	50 (9)	40 (10)
Gender, percent female	68	82 ^a	79 ^a	97 ^a	11 ^a
Education in years, mean (SE)	17 (2)	16 (3) ^{***}	16 (3) ^{***}	15 (2) ^{****}	14 (2) ^{****}
Employed at time of survey, percent	91	17 ^a	31 ^a	26 ^a	54 ^a
Number of doctors consulted for exposure-related conditions, mean (SE)	1.1 (1.7)	11 (17) [*]	11 (8) [*]	15 (4) ^{**}	11 (11) ^{**}
Number of exposure-related hospital visits, mean (SE)	0.1 (0.3)	7 (19)	3 (5)	5 (6)	6 (10)

^a Chi-square with four degrees of freedom (χ^2_4) has $p \leq 0.001$.

^{*} $p \leq 0.05$, ^{**} $p \leq 0.01$, ^{***} $p \leq 0.001$, ^{****} $p \leq 0.0001$ as compared to controls.

**Table 2.** Symptom severity scores by group^a.

Symptoms	Controls	MCS-no event	MCS-event	Implant	Gulf War veterans
Musculoskeletal	2.9 (0.3)	6.4 (0.3)****	7.5 (0.3)****	9.0 (0.2)****	8.1 (0.3)****
Airway/mucous membrane	2.5 (0.3)	6.8 (0.3)****	7.9 (0.3)****	7.7 (0.3)****	7.2 (0.4)****
Heart/chest-related	1.1 (0.3)	4.7 (0.3)****	6.2 (0.3)****	6.4 (0.3)****	5.3 (0.4)****
Gastrointestinal	1.7 (0.3)	6.4 (0.3)****	6.9 (0.3)****	7.8 (0.3)****	6.6 (0.4)****
Cognitive	1.6 (0.3)	7.6 (0.3)****	8.3 (0.2)****	8.4 (0.2)****	6.7 (0.4)****
Affective	2.1 (0.3)	6.6 (0.3)****	7.6 (0.3)****	7.9 (0.3)****	7.2 (0.4)****
Neuromuscular	1.4 (0.3)	5.7 (0.4)****	7.4 (0.3)****	7.8 (0.3)****	6.3 (0.4)****
Head-related	1.9 (0.3)	6.5 (0.4)****	7.4 (0.3)****	7.7 (0.3)****	6.9 (0.4)****
Skin	1.7 (0.3)	4.8 (0.3)****	6.0 (0.3)****	6.7 (0.3)****	6.1 (0.4)****
Genitourinary	1.3 (0.2)	4.7 (0.4)****	6.3 (0.3)****	6.9 (0.3)****	5.0 (0.5)****
Totals (0–100)	18.0 (1.7)	60.1 (2.2)****	71.3 (2.0)****	75.3 (1.9)****	65.4 (2.9)****

^a Individual items scored 0–10, mean and (SE) given in table.

**** $p \leq 0.0001$ as compared to controls.

Controls, who were recruited from professional meetings, had significantly more years of formal education than did patient groups. However, all groups averaged at least 2 years of college. The control group had the highest percentage of persons who were employed at the time of the survey. Nearly everyone in the MCS-no event, the MCS-event, and implant groups, and 86% of the Gulf War veterans said that illness had affected their ability to work, versus 38% of controls. Among the 72 Gulf War veterans, 81% had separated from the military, 42% for health reasons and 39% for reasons unrelated to their health.

Over their lifetimes, individuals in the four patient groups had consulted significantly more physicians for exposure-related conditions, on average 11–15 different physicians versus 1.1 for controls. Patient groups reported more exposure-related hospital visits (total number of emergency room visits and hospitalizations) than did controls, 3–7 versus 0.1. However, due to the large variability in number

of visits, these differences were not statistically significant.

Initial Exposure Events

Patients attributed onset of their illnesses to diverse exposures. For the MCS-event group, the most frequently mentioned initiating events involved exposures to various solvents and cleaners (54%), 'indoor air contaminants' (45%), pesticides (24%), drugs (6%), and fragrances (5%).

Most of the implant patients had received either breast implants (77%) or temporomandibular joint implants (17%). Reasons most commonly given for implantation were improvement of appearance (59%), temporomandibular joint pain or dysfunction (17%), cancer surgery (7%), and fibrocystic disease (6%). Overall, 68% reported rupture of an implant, and 78% had had one or more implants removed. Among those who had undergone explantation, health status following explantation was reported as greatly

Table 3. Severity of chemical intolerances by group^a.

Chemical intolerance	Controls	MCS-no event	MCS-event	Implant	Gulf War veterans
Diesel or gas exhaust	2.3 (0.3)	7.9 (0.3)****	8.1 (0.3)****	6.5 (0.4)****	5.4 (0.4)****
Tobacco smoke	3.5 (0.4)	7.3 (0.3)****	7.5 (0.4)****	6.7 (0.4)****	4.7 (0.4)*
Insecticide	2.7 (0.4)	9.0 (0.2)****	8.8 (0.2)****	7.1 (0.4)****	5.1 (0.5)****
Gasoline	1.7 (0.3)	7.1 (0.3)****	7.7 (0.3)****	6.5 (0.4)****	4.5 (0.5)****
Paint or paint thinner	2.5 (0.3)	8.8 (0.2)****	8.9 (0.2)****	6.9 (0.4)****	4.5 (0.5)****
Cleaning products (disinfectants, bleach)	1.9 (0.3)	8.3 (0.2)****	8.5 (0.2)****	6.9 (0.4)****	4.8 (0.5)****
Fragrances	2.2 (0.3)	8.8 (0.2)****	8.9 (0.2)****	6.8 (0.4)****	4.5 (0.5)****
Tar or asphalt	1.9 (0.3)	7.9 (0.3)****	8.3 (0.3)****	5.8 (0.4)****	3.9 (0.4)****
Nailpolish or hairspray	1.4 (0.2)	8.3 (0.2)****	8.5 (0.3)****	6.3 (0.4)****	4.3 (0.5)****
New furnishings (carpet, shower curtain)	1.4 (0.3)	8.4 (0.3)****	8.6 (0.2)****	5.7 (0.4)****	3.2 (0.4)****
Totals (0–100)	21.3 (2.6)	81.5 (1.6)****	83.0 (1.9)****	63.7 (3.2)****	44.8 (3.8)****

^a Individual items scored 0–10, mean and (SE) given in table.

* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$, **** $p \leq 0.0001$ as compared to controls.

**Table 4.** Severity of other intolerances by group^a.

Other intolerances	Controls	MCS-no event	MCS-event	Implant	Gulf War veterans
Chlorinated tap water	0.4 (0.3)	5.0 (0.3)*	5.6 (0.3)*	4.2 (0.4)*	2.5 (0.4)*
Foods or food additives	1.3 (0.3)	6.3 (0.3)*	6.1 (0.3)*	6.1 (0.3)*	4.2 (0.3)*
Food cravings or feeling ill if meal missed	1.8 (0.3)	5.8 (0.3)*	5.6 (0.3)*	5.9 (0.3)*	4.0 (0.3)*
Feeling ill after meals	1.3 (0.3)	4.0 (0.3)*	4.9 (0.3)*	4.6 (0.3)*	4.5 (0.3)*
Caffeine	1.1 (0.3)	4.7 (0.3)*	4.5 (0.3)*	4.3 (0.3)*	3.7 (0.3)*
Feeling ill if stop or decrease caffeine	2.3 (0.3)	1.5 (0.3)	2.4 (0.3)	3.2 (0.3)	3.6 (0.3)*
Alcohol in small amounts	0.9 (0.3)	4.6 (0.4)****	5.7 (0.4)****	4.8 (0.4)****	3.4 (0.4)****
Fabrics, jewelry, creams, and cosmetics that touch skin	1.2 (0.3)	5.8 (0.4)****	6.2 (0.4)****	5.0 (0.4)****	2.7 (0.4)**
Adverse reactions to drugs or medications	1.4 (0.3)	7.5 (0.4)****	7.2 (0.4)****	7.1 (0.4)****	3.6 (0.4)****
Classical allergic reactions (pollen, dust, mold, dander, insect stings)	3.6 (0.3)	6.3 (0.4)****	6.5 (0.4)****	6.6 (0.4)****	5.4 (0.4)**
Totals (0–100)	15.2 (1.9)	50.3 (2.1)*	53.5 (2.4)*	49.4 (2.5)*	37.4 (3.1)*

^a Individual items scored 0–10, mean and (SE) given in table.

* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$, **** $p \leq 0.0001$ as compared to controls.

improved by 9%, somewhat improved by 36%, unchanged by 13%, somewhat worsened by 18%, and greatly worsened by 24%.

Gulf veterans' duties during deployment included supply, transit, and cargo handling (29%); engineering or construction (13%); maintenance or mechanical work (11%); explosives, demolition, or munitions (8%); police or guard (8%); medical/evacuation (7%); armored vehicles or tanks (7%); operations (7%); and soldier general duties (7%). Duration of service in the Persian Gulf ranged from less than 1 month to 48 months, with a mean of 3 1/2 months. Fifty-four percent of the veterans felt they knew which exposures in the Gulf had caused their illness, while 25% cited no particular exposure, and 19% said they did not know. Exposures most frequently mentioned as initiating illness were oil 'fumes' (26% of all veterans surveyed), drugs or vaccines (10%), contaminated food or water (7%), and pesticides (6%). A few individuals also mentioned fuels, vehicle exhaust, anti-nerve agent drugs, nerve agent, bunker demolition, phosgene or mustard gas, and 'fumes' from SCUD missiles.

Many veterans recalled using insect repellent (81%), taking pyridostigmine bromide (75%, half of whom noted

symptoms while taking the drug), receiving anthrax (72%) or botulinum (50%) vaccines, hearing chemical alarms sound (64%), seeing SCUD missiles overhead or landing nearby (44%), and being exposed to disposal fumes (11%, with 7% specifying bunker demolition and possible nerve agent exposures). Exposures the veterans rated as 'severe' (score of 8, 9, or 10 on 0–10 scale) included exhaust (58%), fuels (54%), oil fire smoke (51%), insect repellents (49%), tent heater smoke (35%), smoke from burning waste (35%), insecticides (32%), contaminated food/water (22%), paints or solvents (21%), and chemical agent-resistant coating used on vehicles (19%).

Although individuals in the MCS-no event group did not attribute onset of their illness to a particular exposure, 68% did mention various factors, exposures, or series of exposures which they felt had contributed to their health problems. These included various chemicals (24%), indoor air contaminants (20%), drugs (9%), stress (7%), pesticides (6%), and illness (6%).

Symptom Severity

Mean total symptom severity scores for all patient groups were significantly greater than for controls (Table 2). Mean

Table 5. Additional items by group^a.

Symptom	Controls	MCS-no event	MCS-event	Implant	Gulf War veterans
Confusion while driving	0.7 (1.8)	5.1 (3.7)****	6.0 (3.6)****	6.6 (3.3)****	4.8 (3.5)****
Sensitivity to bright light	2.0 (2.8)	5.3 (3.5)****	5.6 (3.7)****	6.8 (3.0)****	5.5 (3.7)****
Sensitivity to noise	1.8 (2.6)	5.7 (3.4)****	5.9 (3.4)****	6.6 (3.4)****	5.2 (3.9)****
For Smokers only:	<i>n</i> =7	<i>n</i> =4	<i>n</i> =17	<i>n</i> =27	<i>n</i> =55
Ill if increase tobacco use	2.9 (3.2)	3.5 (4.1)	3.2 (3.8)	3.3 (4.2)	2.9 (3.7)
Ill if decrease tobacco use	3.0 (2.9)	2.0 (4.0)	2.3 (3.0)	4.2 (4.1)	2.9 (3.9)

^a Individual items scored 0–10, mean and (SE) given in table.

**** $p \leq 0.0001$ as compared to controls.

**Table 6.** Life impact of chemical and other intolerances by group^a.

Area of impact	Controls	MCS-no event	MCS-event	Implant	Gulf War veterans
Diet	1.0 (0.3)	7.3 (.3)****	7.3 (0.3)****	5.5 (0.3)****	4.7 (0.3)****
Ability to work or go to school	0.5 (0.3)	9.0 (.3)****	9.0 (0.3)****	7.1 (0.3)****	5.6 (0.3)****
Choice of home furnishings	0.8 (0.3)	8.5 (.3)****	8.0 (0.3)****	5.0 (0.3)****	3.4 (0.3)****
Choice of clothing	1.0 (0.3)	7.7 (.3)****	7.6 (0.3)****	4.9 (0.3)****	3.3 (0.3)****
Ability to drive or travel	0.2 (0.3)	7.3 (.3)****	7.8 (0.3)****	6.1 (0.3)****	4.4 (0.3)****
Choice of personal care products	1.8 (0.3)	9.4 (.3)****	8.8 (0.3)****	6.6 (0.3)****	4.5 (0.3)****
Ability to be around others at social functions	0.6 (0.3)	8.8 (.3)****	8.6 (0.3)****	6.8 (0.3)****	5.3 (0.3)****
Choice of hobbies or recreation	0.6 (0.3)	8.6 (.3)****	8.6 (0.3)****	7.0 (0.3)****	5.1 (0.3)****
Relationships with spouse and family	0.4 (0.3)	7.2 (.3)****	7.8 (0.3)****	6.5 (0.3)****	5.2 (0.3)****
Ability to clean home or maintain yard	0.9 (0.3)	7.8 (.3)****	7.9 (0.3)****	7.5 (0.3)****	5.1 (0.3)****
Totals (0–100)	7.7 (1.7)	81.3 (1.8)****	81.0 (2.3)****	61.7 (3.3)****	45.7 (4.0)****

^a Individual items scored 0–10, mean and (SE) given in table.

* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$, **** $p \leq 0.0001$ as compared to controls.

scores on individual symptom items also were significantly greater for all patient groups than for controls. In general, Gulf War veterans, implant recipients and controls considered muscle and joint symptoms to be their most severe among the ten symptom categories, while both MCS groups rated cognitive difficulties as most severe. Visual comparison of symptom profiles on the target diagram (Figure 1) revealed similar, multi-system patterns for the four patient groups.

Chemical (Inhalant) Intolerances

Mean total chemical intolerance scores for the patient groups were significantly greater than for controls (Table 3). Mean scores for individual exposure items likewise were significantly greater for patients than for controls. While controls attributed their most severe symptoms to tobacco smoke, patients implicated pesticides, paint, fragrances,

cleaning products and, in the case of Gulf War veterans, diesel or gas engine exhaust.

Other Intolerances

Mean total scores on the Other Intolerance Scale for the patient groups were significantly greater than for controls (Table 4). Mean scores on most individual items also were significantly greater for all patient groups than for controls, with the single exception of caffeine withdrawal symptoms for the MCS and implant patient groups. While symptoms associated with classical allergic reactions were considered most severe by controls and Gulf War veterans, adverse reactions to drugs, medications, or medical devices received the highest severity ratings from the implant group and both MCS groups.

All patient groups reported significantly more confusion while driving and heightened sensitivity to light and noise,

Table 7. Masking items by group^a.

Masking item	Controls	MCS-no event	MCS-event	Implant	Gulf War veterans
Tobacco	9	4	13	21*	54****
Alcohol	63	11****	26****	23****	53
Caffeine	86	41****	61***	80	93
Scented personal care products	80	12****	9****	46****	58
Insecticides	64	19****	26****	33****	40**
Chemical or smoke exposure at work	53	32**	44	20****	29**
Second-hand smoke	7	2	4	11	32****
Gas or propane stove	37	31	17**	28	31
Scented fabric softener	78	7****	9****	39****	67
Drugs (steroids, pain relievers, recreational)	11	24*	33***	72****	56****
Mean Masking Index (0–10) ^b	4.9 (SE=0.2)	1.9**** (SE=0.2)	2.4**** (SE=0.2)	3.7**** (SE=0.2)	5.1 (SE=0.2)

^a Percent of each group with ongoing exposure to each item is given in table.

^b Mean masking score (sum of all 'yes' responses, 0–10 possible).

* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$, **** $p \leq 0.0001$ as compared to controls.



than did controls (Table 5). There were no significant differences between patient groups and controls on items asking smokers whether they noticed feeling ill when they increased or decreased their consumption of tobacco products.

Life Impact

The mean total life impact scores for the patient groups were significantly greater than for controls (Table 6). Mean scores on all individual life impact items also were significantly greater for patient groups than for controls. In general, patients felt that their ability to work or go to school, ability to engage in social activities, and choice of hobbies or recreation had been most adversely affected by their sensitivities. In contrast, controls felt that their choice of personal care products (deodorants, makeup) was the aspect of their lives most affected by their chemical intolerances.

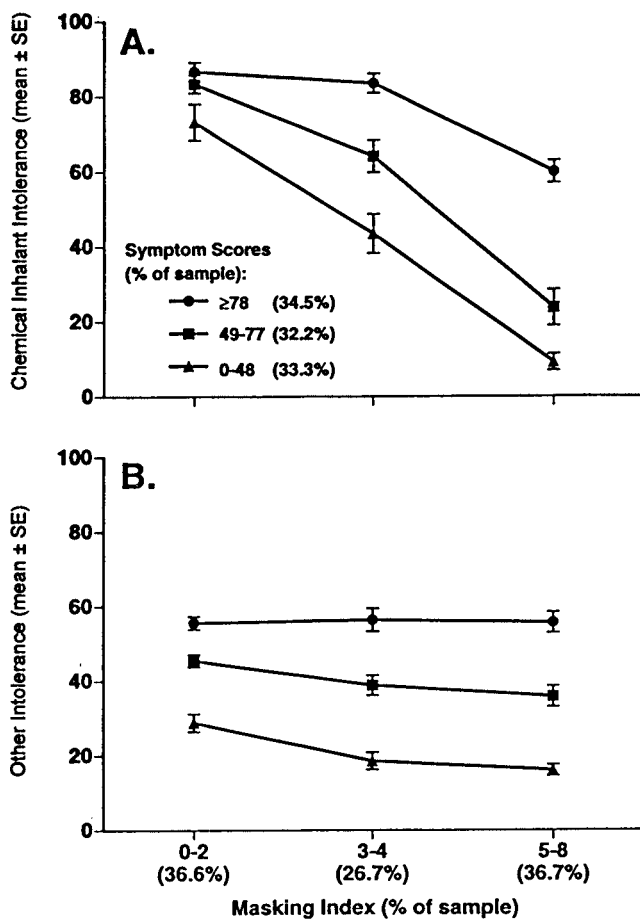


Figure 2. (a and b) Relationship between masking and reporting of chemical intolerances and other intolerances. All 421 subjects were divided into three nearly equal-sized groups by Symptom Severity scores (≥ 78 , 49–77, and ≤ 48). Chemical Intolerance scores (a) and Other Intolerance scores (b) were then plotted against Masking Index

However, the average rating by controls for this item was only 1.8 (on the 0–10 scale), which was well below the ratings given by the patient groups for any item.

Masking

The mean Masking Index for implant recipients and the two MCS groups was significantly lower than that for controls. Masking for Gulf War veterans did not differ significantly from controls (Table 7). The item on the Masking Index most frequently endorsed by all groups was caffeine use (once a week or more often). MCS patients were less likely to use caffeine than other groups. Significantly more Gulf War veterans and implant recipients said they used tobacco at least weekly and significantly more veterans were exposed to second-hand smoke than were controls. The majority of Gulf veterans and controls said they routinely used alcoholic beverages, scented personal care products, and scented fabric softeners in their laundry, while all other patient groups were significantly less likely to use any of these than were controls. Patients in all groups were less likely to have had their homes or workplaces treated for insects in the past year. Drug/medication use by the patient groups was significantly greater than for controls.

The masking by symptoms interaction reached significance for chemical inhalant intolerances ($p=0.0016$), but not for other intolerances ($p=0.0911$). Figures 2 a and b illustrate how masking interacted with subjects' recognition of intolerances even when they reported the same or similar levels of symptoms. The interaction plots show a larger effect of masking when symptoms were less severe and a larger effect on Chemical Inhalant Intolerance scores than on Other Intolerance scores.

Discussion

MCS and the ill-defined illnesses some individuals report following breast or temporomandibular joint implantation or after service in the Gulf War commonly involve symptoms affecting multiple organ systems, and frequently include cognitive and affective difficulties. These conditions also share in common attribution to an antecedent exposure. The fact that persons with these poorly understood conditions report such diverse symptoms, often involving different organ systems, has led some physicians to conclude that none of them rises to the level of a medically identifiable syndrome. Nor are these conditions explained by current, generally accepted mechanisms for disease. In earlier work, we have proposed that the strikingly similar phenomenologies of these illnesses, which emerge in a subset of the population as a sequel to certain chemical exposures, suggest that a new general mechanism



or theory of disease, called 'toxicant-induced loss of tolerance' (TILT), could be operative (Miller, 1997; Ashford and Miller, 1998).

TILT appears to evolve in two stages. The first is loss of prior, innate or natural tolerance for various chemicals, foods, and drugs following acute or chronic exposure to an environmental agent or agents. Events that appear to initiate this process include exposures to pesticides, solvents, contaminated air in a sick building, drugs, and implants. The second stage of TILT involves subsequent triggering of symptoms by previously tolerated amounts of structurally diverse chemicals, foods, drugs, and food/drug combinations, such as caffeine and alcoholic beverages. Overlapping responses to common inhalants and ingestants may result in an individual who feels sick most of the time but is unable to identify the effect of any particular exposure. In essence, these overlapping responses may create a kind of background noise that hides the effect of any particular signal. This phenomenon, coupled with the normal habituation that occurs in response to repeated exposures, has been called 'masking' (Miller, 1997; Miller et al., 1997; Ashford and Miller, 1998). Our findings in this study suggest that masking might affect Gulf War veterans' and implant patients' recognition of the effects of chemical exposures, and that exposure avoidance might be important for their recovery.

Converging lines of evidence support TILT's existence: (1) The fact that similar multi-system illnesses have been reported by investigators from more than a dozen countries in different demographic groups following well-characterized chemical exposure events; (2) the internal consistency of the patients' reports of intolerances not just for chemical inhalants, but also for particular foods, caffeine, alcohol, medications, anesthetic agents, and skin contactants; (3) the parallels between this condition and addiction (Miller, 1999); (4) the identification of an anatomical substrate, the nervous system, whose malfunction might explain these problems; and (5) recent animal models that replicate key features of TILT (Overstreet et al., 1996; Sorg, 1996; Rogers et al., 1999).

The specific mechanism(s) underlying TILT remains to be elucidated. Conceivably, we might be in the early, observational stage of an emerging new theory of disease, much as physicians were with respect to the germ theory prior to the identification of specific microorganisms. In the late 1800s, Koch provided scientists with a set of rigorous criteria for verifying that a particular microorganism caused a particular disease. Likewise, a set of criteria for testing whether everyday environmental exposures trigger symptoms associated with TILT has been published (Miller, 1997; Miller et al., 1997).

Researchers have employed a wide array of case definitions and criteria for enrolling patients in studies of chemical sensitivity (summarized in Ashford and Miller,

1998). In some cases, prospective subjects had only to say that they considered themselves especially sensitive to certain chemicals in order to participate. The EESI offers investigators a multi-dimensional approach for characterizing and classifying individuals according to their sensitivities, and thus facilitates cross-comparison of results from various studies or across different populations, as demonstrated here.

As in our earlier study of 112 persons who attributed onset of MCS to exposure to either pesticides or indoor air contaminants, approximately 80% of the MCS respondents were women (Miller and Mitzel, 1995). Other investigators have noted a similar preponderance of females in their MCS samples (Cullen et al., 1992; Fiedler et al., 1994; Lax and Henneberger, 1995). The larger number of males in our Gulf War veteran group and females in our implant group likely reflects gender ratios in the populations they represent. Overall, there were no significant differences between males and females in terms of health status, symptoms, chemical intolerances, other intolerances, life impact, or masking. Nor were there significant differences between males and females in the MCS and implant groups in these respects. However, female Gulf War veterans reported significantly greater symptom severity (80.1 versus 63.5, $p=0.0245$), chemical intolerances (62.4 versus 42.6, $p=0.0271$), other intolerances (61.0 versus 36.3, $p=0.0005$), and life impact of their sensitivities (66.3 versus 43.7, $p=0.0304$) than did their male counterparts. There were no gender-related differences in health status (2.0 versus 3.2, $p=0.0893$) or masking (5.1 for both) among the veterans.

The average educational level of MCS patients in our sample was about a year greater than that reported in other studies, possibly reflecting a responder bias. Despite their educational attainment, the majority of the MCS and implant patients and almost half of the Gulf War veterans indicated that they were not employed at the time of the survey because of illness.

The high levels of symptoms involving multiple organ systems reported by our patient groups are consistent with findings from other studies involving MCS patients (Cullen et al., 1992; Simon et al., 1993; Lax and Henneberger, 1995), implant recipients with chronic health problems (Brautbar et al., 1992; Hoffman et al., 1995), and sick Gulf War veterans (NIH, 1994; CDC, 1995; Fukuda et al., 1998). The diverse clinical presentations of implant recipients and ill Gulf War veterans and the fact that the majority of persons who have had implants or Gulf War exposures do not report being sick, have led some investigators to conclude that illness, if present, must be unrelated to these exposures. A National Institutes of Health Technology Assessment Workshop on the Persian Gulf Experience and Health concluded that among sick Gulf War veterans, "no single disease or syndrome is apparent, but rather multiple illnesses with overlapping symptoms and causes" (NIH,



1994). We see things differently: most of the Gulf War veterans who are ill exhibit multi-system symptoms and new-onset intolerances, consistent with TILT in civilians. Fukuda et al. (1998) of the Centers for Disease Control and Prevention speculated that the reason for the increased symptoms among the Gulf War veterans was that "key risk factors present among both deployed and non-deployed populations were present at higher intensity or greater frequency among [Gulf War] veterans." Their observations are consistent with the fact that TILT appears to occur in both soldiers and civilians following a wide array of exposures, including pesticides, solvents, and drugs.

Many MCS patients, implant recipients, and Gulf War veterans report symptoms consistent with, and some have been diagnosed with, chronic fatigue syndrome and fibromyalgia. Buchwald and Garrity (1994) compared clinical findings for patients who met criteria for MCS, fibromyalgia, or chronic fatigue syndrome (30 patients per group) and found that patients in these groups had strikingly similar health problems, and that the diagnoses patients received depended more upon their chief complaints and the types of physicians they saw than on the illness process itself.

The veterans and implant patients in our study assigned slightly higher severity ratings to muscle and joint symptoms than did MCS patients, who assigned their highest rating to cognitive difficulties. Possible explanations for these minor differences could be the higher levels of masking in the first two groups, the fact that 17% of our implant patients had experienced temporomandibular joint problems, and the greater physical demands of jobs held by many veterans.

Chemical intolerance scores for the patient groups appeared to be inversely related to their Masking Index (further discussed below). All groups implicated chemically diverse exposures as provoking symptoms. Interestingly, tobacco smoke, which controls said caused their worst symptoms, was ranked last and next to last in severity by the MCS groups. Scores on all of the chemical intolerance items for the patient groups were significantly higher at the $p \leq 0.0001$ level as compared to controls, except for tobacco smoke for the Gulf War veterans where the p value was ≤ 0.05 . The lower level of significance on this item may be related to the fact that 54% of the veterans in our sample were smokers.

Questions on the EESI that asked smokers to rate the severity of their symptoms when they increased or decreased their tobacco usage revealed no differences between smokers in the patient groups versus the control group. Variability in smokers' responses on these items was high and there were few smokers in the MCS groups. Nevertheless, it is possible that affirmative responses to these questions may be helpful for assessing chemical susceptibility on an individual basis. If chemical sensitivity

is related to addiction, as we have suggested (Miller, 1997, 1999), then tobacco dependence may be indicative of chemical susceptibility. In other words, persons who experience severe withdrawal symptoms when they try to quit tobacco may be more chemically sensitive than those able to quit with less difficulty.

Several of the items on the Other Intolerance Scale refer to addiction-like responses or cravings for substances. These questions were included based upon numerous reports by individuals with MCS that chemical exposures trigger food cravings (Miller, 1994); that addiction to the xanthines in coffee, tea, soft drinks, or chocolate is common; that caffeine and alcohol elicit pronounced stimulatory or withdrawal symptoms; and that missing a meal (or quitting particular foods, such as wheat or corn) can precipitate 'withdrawal' symptoms. Randolph and Moss (1980) observed that patients who were 'chemically susceptible' often reported intolerances for sweets or alcoholic beverages, e.g., feeling ill after drinking a single glass of wine or can of beer. They attributed these observations to the relatively rapid uptake of sugars and alcohol from the digestive tract and, consequently, a close temporal association between ingestion and onset of symptoms. Through the use of elimination diets and food challenges, Randolph concluded that alcohol-intolerant patients were intolerant of the foods (grapes, wheat, corn) from which the alcohol was derived. He noted that some individuals who could not drink beer brewed from barley could drink brands brewed from rice.

Ratings for items on the Other Intolerance Scale, with the exception of an item asking about caffeine withdrawal symptoms, were significantly greater for all of the patient groups than for controls. Caffeine withdrawal symptoms were significant for Gulf War veterans, but not for the MCS or implant patient groups. For the MCS groups, this lack of significance might be explained by the fact that significantly fewer MCS patients use caffeine regularly (Table 7, $p \leq 0.001$) and those who do use it regularly may tend to use it sparingly because it makes them feel ill, as evidenced by their higher severity ratings for caffeine-related symptoms on the Other Intolerance Scale. While caffeine use by the implant group did not differ from that of controls, the implant group had the highest percentage of persons using drugs, such as pain relievers and steroids, whose effects may override (mask) awareness of caffeine-related symptoms. In the experience of one of the authors (C.S.M.), some Gulf War veterans continue to drink large quantities of caffeine (5–30 cups of caffeinated beverages per day) in an effort to combat fatigue. Many of these same veterans also report nocturia, anxiety, irritability, headaches, and other symptoms commonly associated with caffeinism. Only by stopping all caffeine use for about a week, observing for withdrawal symptoms, and subsequently reintroducing caffeine, can caffeine intolerance be diagnosed. If this



maneuver were undertaken by Gulf War veterans and implant patients who use caffeine, we suspect that more of them might discover that they are caffeine-intolerant.

In addition to its five scales, the EESI contains items that ask about sensitivity to bright light and noise. Notably, ratings on these items were significantly higher for all patient groups than for controls ($p \leq 0.0001$). Sensitivity to physical agents, such as light and noise, could be due to amplification of sensory signals by the central nervous system; to overreading of external stimuli; or to chemical exposures causing hyperresponsiveness analogous to the photophobia and noise sensitivity that occur during alcohol or drug withdrawal.

Our MCS, implant, and veteran groups reported significantly more mental confusion while driving than did controls ($p \leq 0.0001$ for all comparisons). Difficulty in driving is a frequent complaint of MCS patients. Some have stopped driving for fear of causing an accident, use air purifiers or face masks containing activated charcoal while driving, or avoid heavy traffic. Driving behind diesel vehicles or cars burning oil, and idling in traffic pose major hurdles for some MCS patients. In the experience of one of the authors (C.S.M.), many Gulf War veterans also report spaciness, difficulty concentrating, and confusion while driving, e.g., missing or misinterpreting traffic signals, confusing the foot pedals or shift positions on their vehicles, getting lost while driving in familiar areas, inability to remember directions, forgetting where they are going or where they parked the car, and neglecting to pay the cashier or replace the gas cap after filling the gas tank. A study by Kang and Bullman (1996) of the Department of Veterans' Affairs found a small but significant excess of deaths among Gulf War veterans as compared to other veterans. Notably, these excess deaths were primarily caused by accidents, especially motor vehicle accidents. The authors suggested these deaths might be explained by increased risk-taking behavior, post-traumatic stress disorder, or depression. We propose another possibility: traffic exhaust, gasoline vapors, outgassing from plastic interiors, and other exposures associated with driving may cause cognitive difficulties that are responsible for the increased motor vehicle deaths among Gulf War veterans.

Our findings also suggest an inverse relationship between masking and self-reported chemical intolerances. For a given level of symptoms, the likelihood of an individual's reporting chemical intolerances decreased as masking increased. Several interpretations are possible. First, individuals who feel they are chemically intolerant are apt to avoid more exposures than those who feel they are not. Another possibility is that persons who have more ongoing exposures (e.g., they smoke, use alcohol, caffeine, fragrances) might be less able to *recognize* the effects of particular exposures and therefore would report fewer chemical intolerances. Both factors might also operate

simultaneously. It is not possible to determine the relative contributions of these from the data presented here. It is clear, however, that MCS patients, implant patients, and some Gulf War veterans report similar symptoms, but differ with respect to masking. The question is: does masking impair recognition of triggering exposures? Double-blind, placebo-controlled challenge studies conducted in an environmentally controlled hospital unit, as proposed elsewhere, could help resolve this question (Miller, 1997; Miller et al., 1997).

A recent study of Gulf War veterans conducted by the Centers for Disease Control and Prevention identified smoking as a major risk factor for illness (Fukuda et al., 1998). Consistent with these findings, the mean health status rating (0–10) for Gulf War veterans in our sample was significantly lower for smokers than non-smokers (mean health status of 2.0 and 4.4, respectively, $p=0.0001$). Gulf War veteran smokers also had significantly higher Other Intolerance scores (45.6 versus 28.4, $p=0.0037$) and higher Chemical Inhalant Intolerance scores (52.4 versus 35.3, $p=0.0065$) than did non-smoking veterans. There were no significant differences between smokers and non-smokers in our other study groups with respect to symptoms, chemical intolerances, or other intolerances.

The EESI proved to be useful for comparing the five populations in this investigation. Items on the EESI were derived from extensive data collected for 112 self-described MCS patients who attributed onset of their illness to a well-defined chemical exposure event (Miller and Mitzel, 1995). As such, this instrument embodies five dimensions relevant to chemical sensitivity, providing single numbers representative of symptom severity, chemical inhalant intolerances, other intolerances, life impact, and masking. A companion paper in this volume discusses limitations of this study (Miller and Prihoda, 1999).

When selecting an instrument to collect data, investigators must weigh the validity, reliability, sensitivity, and specificity of available measurement tools. Other published instruments for measuring chemical sensitivity focus on one or two dimensions, such as responses to selected chemicals (Kipen et al., 1995; Bell et al., 1996) or lifestyle limitations as a consequence of sensitivities (Simon et al., 1990). Some of these instruments can be useful for screening large populations. The QEESI offers a more global, quantitative assessment that can be used for both screening and evaluation in research and clinical populations. Researchers might also opt to use the QEESI's ten-item Chemical Inhalant Intolerance Scale *by itself* as a screening instrument (sensitivity of 83.2% and specificity of 84.2%, based on the cutpoint ≥ 40). For other research and clinical applications, the 50-item QEESI offers the advantages of measuring all five dimensions described in this paper and having known validity and reliability. The EESI, which contains additional items concerning employment status, antecedent exposures,



and medical history, might be reserved for detailed clinical evaluations or research studies.

Acknowledgments

Research for this paper was supported in part by an appointment of the first author (C.S.M.) to the Agency for Toxic Substances and Disease Registry (ATSDR) Clinical Fellowship Program in Environmental Medicine, administered by Oak Ridge Associated Universities through an interagency agreement between the U.S. Department of Energy and ATSDR. The authors thank George Freeman and John Adams for their dedicated assistance in preparing and analyzing the data for this manuscript.

References

- Ashford N., and Miller C. *Chemical Exposures: Low Levels and High Stakes*. Wiley and Sons, New York, 1998.
- Ashford N., Heinzow B., Lütjen K., Marouli C., Mølhav L., Mönch B., Papadopoulos S., Rest K., Rosdahl D., Siskos P., and Velonakis, E. Chemical sensitivity in selected European countries: an exploratory study. A report to the European Commission, 1995.
- Bell I., Miller C., Schwartz G., Peterson J., and Amend D. Neuropsychiatric and somatic characteristics of young adults with and without self-reported chemical odor intolerance and chemical sensitivity. *Arch. Environ. Health* 1996; 51 (1): 9–21.
- Brautbar N., Vojdani A., and Campbell A. Multiple chemical sensitivity—fact or myth? *Toxicol. Ind. Health* 1992; 8 (6): v–xiii.
- Buchwald D., and Garrity D. Comparison of patients with chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivities. *Arch. Int. Med.* 1994; 154: 2049–2053.
- Centers for Disease Control and Prevention (CDC). Unexplained illness among Persian Gulf War veterans in an Air National Guard unit: preliminary report. *MMWR* 1995; 44 (23): 443–447.
- Cullen M., Pace P., and Redlich C. The experience of the Yale Occupational and Environmental Medicine Clinics with multiple chemical sensitivities, 1986–1991. *Toxicol. Ind. Health* 1992; 8: 15–19.
- Environmental Protection Agency (EPA). Report to Congress on Indoor Air Quality, Volume II, Assessment and Control of Indoor Air Pollution, 1989.
- Fiedler N., Kipen H., Deluca J., Kelly-McNeil K., and Natelson B. Neuropsychology and psychology of MCS. *Toxicol. Ind. Health* 1994; 10 (4/5): 545–554.
- Fukuda K., Nisenbaum R., Stewart G., Thompson W., Robin L., Washko R., Noah D., Barrett D., Randall B., Herwaldt B., Mawle A., and Reeves W. Chronic multi-system illness affecting Air Force veterans of the Gulf War. *JAMA* 1998; 280(11): 981–988.
- Hoffman D., Stockdale S., Hicks L., and Schwanager J. Neurocognitive symptoms and quantitative EEG results in women presenting with silicone-induced autoimmune disease. *Int. J. Occup. Med. Toxicol.* 1995; 4 (1): 91–98.
- Kang H., and Bullman T. Mortality among U.S. veterans of the Persian Gulf War. *New Engl. J. Med.* 1996; 335 (2a): 1498–1504.
- Kipen H., Hallman W., Kelly-McNeil K., and Fiedler N. Measuring chemical sensitivity prevalence: a questionnaire for population studies. *Am. J. Public Health* 1995; 85 (4): 574–577.
- Kruetzer R., and Neutra R. Evaluating individuals reporting sensitivities to multiple chemicals. Agency for Toxic Substances and Disease Registry, National Technical Information Service, Springfield, VA. Publication #P896-187646, 1996.
- Lax M., and Henneberger P. Patients with multiple chemical sensitivities in an occupational health clinic: presentation and follow-up. *Arch. Environ. Health* 1995; 50 (6): 425–431.
- Meggs W., Dunn K., Bloch R., Goodman P., and Davidoff L. Prevalence and nature of allergy and chemical sensitivity in a general population. *Arch. Environ. Health* 1996; 51 (4): 275–282.
- Miller C. White paper: chemical sensitivity: history and phenomenology. *Toxicol. Ind. Health* 1994; 10 (4): 253–276.
- Miller C. Toxicant-induced loss of tolerance—an emerging theory of disease? *Environ. Health Perspect.* 1997; 105 (suppl 2): 445–453.
- Miller C. Are we on the threshold of a new theory of disease? Toxicant-induced loss of tolerance and its relationship to addiction and abidction. *Toxicol. Ind. Health* 1999; 284–294.
- Miller C., and Mitzel H. Chemical sensitivity attributed to pesticide exposure versus remodeling. *Arch. Environ. Health* 1995; 50 (2): 119–129.
- Miller C., and Prihoda T. The Environmental Exposure and Sensitivity Inventory (EESI): a standardized approach for measuring chemical intolerances for research and clinical applications. *Toxicol. Ind. Health* 1999; 370–385.
- Miller C., Ashford N., Doty R., Lamielle M., Otto D., Rahill A., and Wallace L. Empirical approaches for the investigation of toxicant-induced loss of tolerance. *Environ. Health Perspect.* 1997; 105 (suppl 2): 515–519.
- National Institute of Health (NIH). Technology assessment workshop panel. The Persian Gulf experience and health. *JAMA* 1994; 272: 391–395.
- Overstreet D., Miller C., Janowsky D., and Russell R. Potential animal model of multiple chemical sensitivity with cholinergic supersensitivity. *Toxicology* 1996; 111: 119–134.
- Randolph T. *Environmental Medicine: Beginnings and Bibliographies of Clinical Ecology* (1987). Clinical Ecology Publications, Fort Collins, CO, 1987.
- Randolph T., and Moss R. *An Alternative Approach to Allergies*. Lippincott and Crowell, New York, 1980.
- Rogers W., Miller, C., and Bunegin L. A rat model of neurobehavioral sensitization to toluene. *Toxicol. Ind. Health* 1999; 295–304.
- Simon G., Katon W., and Sparks P. Allergic to life: psychological factors in environmental illness. *Am. J. Psychiatry* 1990; 147: 901–906.
- Simon G., Daniell W., Stockbridge H., Claypoole K., and Rosenstock L. Immunological, psychological, and neuropsychological factors in multiple chemical sensitivity: a controlled study. *Ann. Int. Med.* 1993; 19 (2): 97–103.
- Sorg B. Proposed animal model for multiple chemical sensitivity in studies with formalin. *Toxicology* 1996; 111: 135–145.

