

# Chemical Sensitivity: The Scientific Literature

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This article provides an overview of the scientific literature in which chemically sensitive patients have been directly evaluated. For that purpose, consideration of various case definitions is offered along with summaries of subjects' demographic profiles, exposure characteristics, and symptom profiles across studies. Controlled investigations of chemically sensitive subjects without other organic illnesses are reviewed. To date, psychiatric, personality, cognitive/neurologic, immunologic, and olfactory studies have been conducted comparing subjects with primary chemical sensitivity to various control groups. Thus far, the most consistent finding is that chemically sensitive patients have a higher rate of psychiatric disorders across studies and relative to diverse comparison groups. However, since these studies are cross-sectional, causality cannot be implied. Demonstrating the role of low-level chemical exposure in a controlled environment has yet to be undertaken with this patient group and is crucial to the understanding of this phenomenon. — *Environ Health Perspect* 105 (Suppl 2):409–415 (1997)

Key words: chemical sensitivity, psychiatric, neurologic, olfaction, immune, unexplained symptoms

## Background and Introduction

Exposure to chemicals contained in products such as perfumes, household cleaners, and petroleum-based products has been considered safe and often pleasant. However, reports of unusual sensitivity and illness in response to such items have increased. For example, in the occupational literature, Schottenfeld and Cullen (1) first described a group of patients who became ill following exposure and who later developed medically unexplained symptoms triggered by events (e.g., exposure to odors such as perfumes) that reminded them of their exposure-related illness. Schottenfeld and Cullen described this reaction as an anxiety response, i.e., typical and atypical post-traumatic stress disorder, rather than a heightened physiological sensitivity to chemicals. Several other investigators have suggested that sensitivity to low-level chemical exposures is the modern expression of

well-known psychiatric disorders such as anxiety, depression, or somatization (2,3). A growing debate has arisen between those who regard chemical sensitivity as a disorder mediated by psychiatric factors in a manner similar to conditioned responses and those who see it as a genuine physical susceptibility to low-dose exposures presumed safe. In 1987, Cullen edited a state of the art review for occupational medicine on multiple chemical sensitivities (MCS) in which he suggested a case definition to promote commonality among cases. This definition also attempted to distinguish MCS, at least conceptually, from traditional occupational disease and psychiatric illness. The following components were proposed: initial symptoms acquired in relation to an identifiable environmental exposure(s); symptoms that involve more than one organ system; symptoms that

recur and abate in response to predictable stimuli; symptoms elicited by low-level exposures to chemicals of diverse structural classes; and inability to explain symptoms by standard tests of organ-system function.

Decades prior to the recognition of MCS in the occupational health literature, clinical ecologists or environmental physicians suggested that exposure to levels of chemicals most of the population tolerates may produce symptoms and illness in susceptible individuals (4). However, those physicians cast a much wider net to attribute many defined pathologic illnesses such as cancer, arthritis, and vasculitis to chemical exposures (5). They invoked the general adaptation syndrome model of stress, proposed by Selye (6), to explain the health effects of chemical exposures. That is, normally the organism adapts to a stressor (chemical) even though symptoms may be triggered. With repeated exposure, however, the organism's ability to adapt becomes compromised, leading ultimately to end-organ failure or disease. Genetic and psychosocial factors contribute to individual susceptibility to illness resulting from stress or chemical exposures. Hence, individual differences mediate the ability to tolerate chemical exposures.

The ecologic conceptualization of chemical sensitivity suggests that patients classified by Cullen's criteria would represent only a highly selective subset of patients in the earliest stages of chemical sensitivity since, by definition, no standard test of organ system function can explain symptoms. Thus, known organ dysfunction and traditional disease states are excluded from MCS as defined by Cullen in 1987 (7).

The contrasting paradigms described above will significantly affect subject selection and thus alter the scope and interpretation of research investigations into MCS. In many ways, researchers from these two perspectives are studying different phenomena. Under the paradigm of clinical ecology, the question of concern is the interaction of individual susceptibility with chemical exposures in producing not only chemical sensitivity but also pathologic illnesses. Sensitivity to chemicals, even if not fully appreciated by the patient, is expected to precede and contribute to many known illnesses. In contrast, the traditions of occupational health and toxicology are asking whether such a phenomenon as hypersensitivity to low-level chemical exposures can be documented; and if so, what are the

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Abbreviations used: EEG, electroencephalogram; EMG, electromyogram; MCS, multiple chemical sensitivity; MEK, methyl ethyl ketone; MMPI-2, Minnesota Multiphasic Personality Inventory; PEA, phenyl ethyl alcohol; PET, positron emission tomography; PYR, pyridine; SPECT, single photon emission computed tomography.

mechanisms and implications for treatment and policy.

In the investigation of chemical sensitivities, it is critical to clarify subject selection criteria. The purpose of the workshop reported here was to develop experimental approaches for testing the relationship between low-level chemical exposure and symptomatology among chemically sensitive individuals. In other words, is there a subset of patients who, when exposed to levels of chemicals well below accepted standards tolerated by most individuals, will exhibit symptomatology that can be quantified objectively? Patients who have developed pathologic medical illness such as rheumatoid arthritis may also have chemical sensitivities preceding and concurrent with their illness. However, including patients with diverse medical conditions along with those who have no defined pathology makes it difficult to develop uniform protocols with objective measures that will apply across subjects. Therefore, at the outset it may be most fruitful to begin with a definition of chemical sensitivity that selects patients who do not have other medical illness (7). In light of the need to establish common ground for discussion, the following summary of the literature is focused on investigations of patients who report a symptomatic intolerance for low-level chemical exposures expressed as symptoms reflective of multiple organ systems but who do not have other medical illnesses that might explain their symptoms. The primary question addressed in these investigations is whether any psychosocial or biologic variables can be discovered that would explain these unexpected sensitivities.

**Demographic and Case Characteristics**

Table 1 summarizes demographic information presented by investigators of patients with chemical sensitivities. Despite discrepancies in case selection criteria, the demographic profile of the patient groups is strikingly consistent. The average age is in the fourth decade with a ratio of women to men of approximately 8:2. The average educational level for subjects is at least 2 years of college.

A subset of investigators provided specific information about onset of chemical sensitivity symptoms for their subjects (8–10). To regard chemical sensitivity as acquired suggests that there is a date or time period of onset. However, for a significant subset [39% (8); 38% (10)], onset was reported as gradual and no specific

event or exposure could be recalled (Table 2). For these patients identifying duration of illness becomes difficult. Several investigators summarized the initiating exposure events reported by the subjects. With the exception of Simon et al. (9) and Miller and Mitzel (12), initiating events were highly varied within and between subject groups (Table 3). In the Simon et al. study (9), subjects were recruited from one aerospace manufacturing workplace in which worker compensation claims were being evaluated. Miller and Mitzel (12), in a questionnaire study, included only subjects who could recall a specific organophosphate exposure or remodeling event after which chemical sensitivities developed. Subjects who could not recall one of these events at a specific time were not included.

The remaining studies selected subjects from the community or recruited subjects from physicians who were evaluating or treating their chemical sensitivities. In these studies, a subset of subjects reported events other than chemical exposures as precipitating their sensitivity. For example, Terr (13), Stewart and Raskin (3) and Black et al. (2) included subjects who reported such precipitators as stress, antibiotics, and candidiasis. Studies by Terr (13), Simon et al. (9), and Stewart and Raskin (3) were dominated by subjects involved in litigation related to exposures. As can be seen from the exposure situations, no single chemical or psychosocial situation can be identified as more prevalent than another for the onset of chemical sensitivities. This suggests that the environment, per se, may not be

**Table 1.** Demographic profiles of MCS study subjects.

Study, reference no.	No.	Age <sup>a</sup>	Gender %		Education level <sup>a</sup>
			Female	Male	
Stewart and Raskin (3)	85	38	83	17	83% well educated
Doty et al. (8)	18	46.1 ± 11.2	67	33	15.1
Terr (13)	90	39.5 range 20–63	70	30	Not given
Black et al. (2)	26	49.1 ± 13.0	88	15	14.6 ± 2.6
Simon et al. (9)	13				
Staudenmeyer (19)	58	40.2 ± 10.2	71	29	Not Given
Buchwald and Garrity (11)	30	40.8	77	23	14.8
Miller and Mitzel (12)	112	47.7 ± 9.1	79.5	20.5	15.9 ± 3.1
Simon (5)	41	46.4 ± 9.5	85	15	14.6 ± 2.7
Fiedler et al. (10)	23	42.9 ± 9.5	83	17	14.6 ± 2.5

<sup>a</sup>Values given as mean ± SD.

**Table 2.** Illness profile of chemical sensitivity subjects.

Study, reference no.	Initiating chemical exposure		Duration of illness, years Mean ± SD	Multiple organ systems	
	No.	% of total		No.	% of total
Stewart and Raskin (3)	12	(67)	2 ± 1.4		Not given
Doty et al. (8)	11	(61)	15.6 ± 6.3	16	(88.9)
Terr (13)	90 <sup>a</sup>		Not given	62	(69)
Black et al. (2)	20	(77)	Not given		(100)
Simon et al. (9)	13	(100)	Not given		Not given
Miller and Mitzel (12)	112	(100)	7.7		(100)
Fiedler et al. (10)	37	(62)	4.5 ± 5.2		(100)

<sup>a</sup>Work-related cause for all patients.

**Table 3.** Chemical and other exposures precipitating illness.

Study, reference no.	Source of exposure
Stewart and Raskin (3)	Insecticide, fumes, food additives, candidiasis, antibiotics
Terr (13)	59 overlapping exposures: organic solvents, pesticides, food, dust, stress
Simon et al. (9)	One exposure of new composite plastic: phenol, formaldehyde, MEK
Black et al. (2)	5 exposure categories: fumes at work/home, pesticides, oral contraceptive/pregnancy, stress, antibiotics
Meggs and Cleveland (23)	Organophosphates, volatile organic compounds, lead solder, epoxy resins
Miller and Mitzel (12)	2 exposure categories: organophosphate, remodeling
Fiedler et al. (10)	Chemicals (solvents, paint, spray mount, pesticides), carpet/carpet adhesive, indoor air, medication

the only significant risk factor. Rather, an interaction between individual difference variables and an exposure may produce the risk for symptomatic chemical sensitivities.

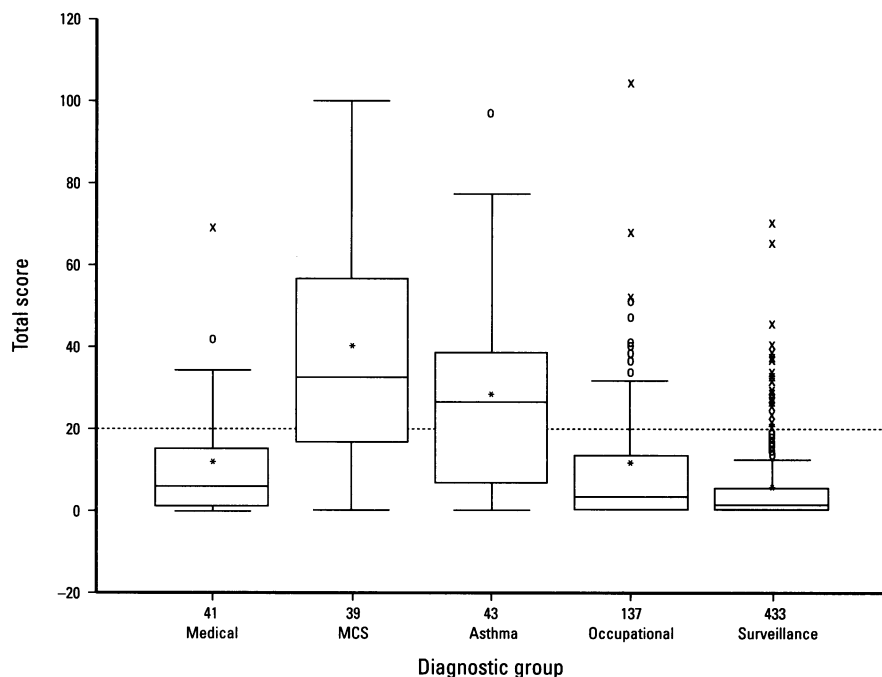
Unlike the majority of studies cited above, subjects in a study by Simon et al. (9) were identified from worker's compensation cases following an outbreak of illness among a group of plastics workers from the aerospace industry. Therefore, it was assumed that these workers ( $n = 13$ ) all had a similar initiating exposure. The authors reported that complaints of symptoms occurred in response to the introduction of a new composite plastic material into the manufacturing process. The principal components of this material were phenol, formaldehyde, and methyl ethyl ketone (MEK). Exposure measurements did not find levels that approached established thresholds.

Explicit in the varying definitions of chemical sensitivities is the concept that multiple chemicals at low levels produce symptoms. Kipen et al. (14), using a modified version of the Randolph environmental questionnaire, found that chemically sensitive subjects reported significantly more substances that made them ill than did either healthy or sick controls (Figure 1). Women reported more substances than men, independent of health status.

While most investigators imply that chemically sensitive patients have symptoms representative of multiple physiologic systems, not all reported on the organ systems or symptoms. Table 4 gives a sample of the percentage of subjects reporting symptoms in each organ system (2,8,10). Across studies, symptoms were most prevalent in the central nervous (neurologic, psychiatric), respiratory, and gastrointestinal systems. However, to date no coherent pattern of symptoms distinguishes chemical sensitivity. Preliminary studies show neurologic, cognitive, and emotional symptoms are the best discriminator between MCS and normals.

## Psychiatric Disorders

Since chemical sensitivity does not readily fit existing paradigms for the relationship between exposure and symptoms, the psychiatric status of patients has been investigated more frequently than that of any of the organ systems. The Axis I psychiatric disorders most prevalent among the MCS patients evaluated are the affective and anxiety disorders (Table 5). With the exception of Stewart and Raskin (3), no investigators have reported current or previous psychoses among MCS patients, although we and others intentionally excluded such subjects.



**Figure 1.** Symptomatic substance scores, by diagnostic group. Box and whisker plots of symptomatic scores are shown for each diagnostic group. Patients with MCS and those with asthma had scores that were significantly elevated over all others although a number of positive scores occurred in all groups. The lower boundary of each box represents the 25th percentile, the upper boundary represents the 75th percentile, and horizontal lines represent medians. \*, group mean; o, group outlier; x, extreme value for group; -----, cutoff score for a positive test.

**Table 4.** Symptom profile of chemical sensitivities.

Study, reference no.	Percent of subjects reporting symptoms				
	CNS	Respiratory	Gastrointestinal	Cardiovascular	Endocrine
Doty et al. (8)	88.9	66.7	66.7	27.8	22.2
Black et al. (2), initial symptoms	Neuro = 38 Psych = 27	58.0	12.0	Not given	Not given
Fiedler et al., unpublished data	91.0	83.0	83.0	83.0	Not given

CNS, central nervous system.

Substance abuse was also rare. Diagnosing somatization disorder was problematic since many symptoms were attributed to chemical sensitivities. Therefore, the percentage of patients who can be considered positive for somatization disorder varies depending on whether or not MCS was accepted as an organic explanation for a physical symptom. Subject selection criteria may also have significantly impacted the outcome on measures of psychiatric disorders. For example, Fiedler et al. (10) found a significantly higher rate of psychiatric disorders among patients who did not have a date of onset for their chemical sensitivities (Table 6). Similarly, Stewart and Raskin (3) and Simon et al. (9) found the highest

rates of psychiatric disorders relative to other studies. Patients in these studies were referred by physicians for psychiatric evaluation (3) or were involved in litigation such as worker's compensation (9). Therefore, the referral process may have biased subject selection toward a higher prevalence of psychiatric disorder. Studies recruiting subjects based on defined criteria found that from 56 to 75% (16 and 11 patients, respectively) did not qualify as having any current psychiatric disorder. Approximately 50% of subjects met criteria for an Axis I psychiatric disorder at some point in their lifetime (10,15,16).

The rate of Axis II personality disorders has been less frequently evaluated. Black

**Table 5.** Psychiatric profile of sensitivity patients.

Study, reference no.	Affective disorders		Anxiety disorders		Psychoses		Somatization disorder		Personality disorder		Substance abuse		Any Axis I diagnosis	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Stewart and Raskin (3)	3	(17)	4	(22)	3	(17)	5	(28)	—	—	—	—	—	—
Black et al. (2)														
Lifetime-DIS	9	(39)	10	(43)	—	0	4	(17)	17	(73.9)	1	(4)	15	(65)
Simon et al. (9)														
Current-DIS	12	(92)	—	—	—	0	0	—	—	—	—	—	—	—
Pre-existing condition	7	(54)	—	—	—	0	9	Somatic trait= (69)	—	—	—	—	—	—
Simon et al. (15)														
Current-DIS	12	(29)	14	(34)	—	0	—	—	—	—	—	—	18	(44)
Pre-existing condition	16	(47)	5	(15)	—	0	9	(26)	—	—	—	—	16	(47)
Fiedler et al. (10)														
Current-DIS	4	(17)	—	0	—	0	3	(14)	—	—	—	0	6	(26)
Lifetime-DIS	7	(30)	2	(9)	—	0	3	(14)	—	—	—	0	10	(43)

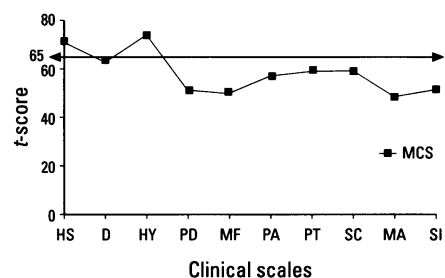
DIS, diagnostic interview schedule.

**Table 6.** Lifetime psychiatric diagnoses.

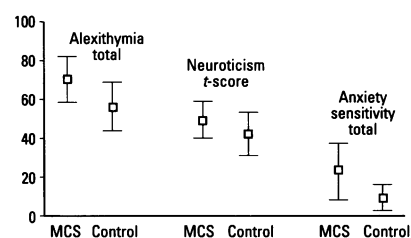
Diagnosis	Multiple chemical sensitivities		Chemical sensitivities (no onset)		Chronic fatigue syndrome		Normals		p
	No.	%	No.	%	No.	%	No.	%	
Depression	7/23	(30)	7/13	(54)	12/18	(67)	11	2/18	0.003
Anxiety	2/23	(9)	4/13	(31)	5/18	(28)	1/18	(6)	0.11
Prescription drug abuse	—	(0)	—	(0)	2/18	(11)	—	(0)	0.15
Bulimia	—	(0)	1/13	(8)	—	(0)	—	(0)	0.18
Somatization disorder	3/22	(14)	1/10	(10)	2/17	(12)	—	(0)	0.37
Total lifetime psychiatric diagnoses	10/23	(43)	9/13	(69)	13/18	(72)	2/18	(11)	0.004

et al. (16) reported that 75% of his sample met the criteria for a personality disorder based on a structured interview. Several studies have used questionnaires to evaluate traits associated with somatic symptoms. For example, Fiedler et al. (10) reported Minnesota Multiphasic Personality Inventory (MMPI-2) group data consistent with somatoform disorders (Figure 2). Other studies using the Symptom Checklist-90, a list of 90 symptoms associated with psychiatric disorders, revealed significantly higher rates of depression (15,16), somatization (9,15,16), and anxiety (16) [phobic anxiety; Simon et al. (15)] than control subjects. Several studies have found significant differences from controls on the Whately Index, an illness behavior questionnaire (9,16), and on the Barsky Amplification Scale, a scale associated with somatic symptoms (9). In composite, MCS subjects relative to controls tend to report a higher number of physical symptoms and score higher on scales that reflect concerns with somatic sensations. Preliminary data from our current study also support sensitivity in response to the physical sensations of anxiety (Figure 3).

Regardless of the control groups chosen, as a group chemically sensitive subjects have significantly more psychopathology. A portion of this pathology may be explained by the higher prevalence of somatic symptoms, which most subjects associate with sensitivities to chemicals. However, Staudenmayer et al. (17) reported a significantly higher rate of physical and sexual abuse among universal reactors. Universal reactors were identified based solely on the attribution of symptoms to multiple chemicals and were compared to a group of patients with multiple chronic symptoms accompanied by an Axis I psychiatric disorder. Unlike all other cross-sectional studies of chemically sensitive subjects, Staudenmayer et al. reported on a group of subjects who were in ongoing psychotherapy. Therefore, the context in which subjects were evaluated and the nonspecific case criteria may have biased subject selection toward a more psychological explanation for symptoms. On the other hand, investigators such as Bell et al. (18) suggest that chemical sensitivities may arise from an interaction of psychological stress and chemical exposures. Subjects



**Figure 2.** MMPI-2 mean t-scores. MMPI, clinical scale names: HS, hypochondriasis; D, depression; HY, conversion hysteria; PD, psychopathic deviate; MF, masculinity/femininity; PA, paranoia; PT, psychasthenia; SC, schizophrenia; MA, hypomania; SI, social introversion.



**Figure 3.** Personality variables. Controls are significantly different from MCS on all measures. Mean ± SD; n = 23; control n = 13.

studied by Staudenmayer et al. (17) may represent this complex interaction.

In spite of the elevated rate of psychopathology among groups of chemically sensitive subjects, a significant percentage of patients do not meet criteria for any current or lifetime psychiatric diagnosis. The variability in psychiatric status among subjects reporting chemical sensitivities suggests that current and previous psychiatric status will be an important covariate in the study of chemical sensitivities.

**Table 7.** Neuropsychologic results of chemical sensitivity.

Study, reference no.	Attention	Verbal memory	Visual memory	Visuomotor speed	Mental flexibility
Simon (15)	NS	Rey auditory, post distraction trial Logical memory, immediate	NS	NS	NS
Fiedler et al. (10)	NS	NS	Continuous visual memory test, false alarms	NS	NS

NS, not significant.

## Neuropsychologic Evaluation

To date, two controlled studies have appeared in which a standardized neuropsychologic evaluation was reported (Table 7). Neither study reported neuropsychologic deficits that could be regarded as significant after taking into account multiple comparisons. Simon et al. (15) reported significant differences on some measures of verbal memory but they were not significant after adjusting for indices of psychologic distress. Fiedler et al. (10) reported significant reduction in performance on one aspect of a visual memory task. However, no differences were seen on other tasks of visual memory. Thus, despite numerous cognitive complaints, neuropsychologic testing does not substantiate cognitive deficits when MCS patients are evaluated without control of the exposure condition.

## Neurophysiology of MCS

Few controlled studies have been conducted in which neurophysiologic measures such as electroencephalograms (EEG), single photon emission controlled tomography (SPECT), and positron emission tomography (PET) have been used to evaluate MCS. In one controlled study, Staudenmayer and Selner (19) reported that more chemically sensitive ("universal reactors") and psychologic subjects were classified as having higher EEG  $\beta$ -activity during relaxation than controls. Chemically sensitive subjects also had higher levels of electromyogram (EMG) scalp activity than either normal or psychologic subjects. No differences were observed between the groups for peripheral temperature or skin resistance while relaxing. The authors report these findings in support of the psychosomatic hypothesis of intolerance to environmental chemicals. Both the psychologic and MCS groups included a wide range of psychologic disorder (e.g., multiple personality disorder, depression, panic). The authors reported that 50% of the MCS group, who were willing to accept psychologic intervention,

had various psychiatric diagnoses, but the diagnoses were not given. This information suggests that the only difference between the psychologic and the MCS groups was the attribution of illness to chemicals or environmental exposures. Thus, the similarities found between the groups were not surprising.

While other investigators, e.g., Rea (20), have reported the use of SPECT and PET for evaluation of chemically sensitive patients, no controlled studies have yet appeared in the literature.

## Controlled Challenges

Environmental physicians or clinical ecologists and Selner and Staudenmayer (21) have reported controlled challenge studies of chemically sensitive or environmentally allergic patients. These investigators use the word control to describe the use of masking and placebos. However, no study has appeared in the literature in which normal controls, matched on appropriate demographic variables, have also been challenged or exposed under the identical protocol. Such controlled studies are sorely needed and their design is the subject of the present workshop.

## Nasal Pathology and Olfaction

MCS patients often report heightened odor sensitivity (10). Researchers have conceptualized that this sensitivity would be expressed in reduced odor threshold. Doty et al. (8) found no significant differences between MCS and age and sex matched normal controls in their ability to detect phenyl ethyl alcohol (PEA) or MEK. Similarly, in standard odor-detection testing, Fiedler et al. (22) also found no significant difference between normal controls and MCS subjects in thresholds for PEA or pyridine (PYR). At suprathreshold concentrations of PEA, MCS subjects reported significantly more trigeminal symptoms (e.g., burning, stinging) and rated PEA as more unpleasant and unsafe than did normals.

These differences between MCS and normals were not observed for PYR, a known unpleasant, trigeminal stimulant. Fiedler et al. (10) also found no differences in performance on the University of Pennsylvania Smell Identification Test, a multiple-choice test that assesses the ability to identify 40 odors.

With regard to nasal pathology, Doty et al. (8) found that relative to controls, MCS had an overall increased resistance before and after threshold testing. Both MCS and controls also had increased nasal resistance following threshold testing for MEK. Meggs et al. (23), in an uncontrolled study, reported that 100% ( $n=10$ ) of the MCS patients evaluated had abnormal rhinolaryngoscopic findings including edema, excessive mucous, and cobblestone appearance of posterior pharynx and base of the tongue. Kehrl et al. (personal communication) in another uncontrolled study reported frequent nasal pathology in their MCS subjects. These findings suggest that MCS subjects do not necessarily detect odors at lower concentration, but they may respond more markedly with symptoms once odors are detected. How this relates to observations of nasal pathology remains to be explored, although altered breathing patterns and neurogenic inflammation have been suggested. The rate of nasal pathology, however, must be evaluated relative to appropriate controls.

## Immune Function

A number of authors have described immunologic laboratory abnormalities in chemically sensitive individuals. All but one are case series or cross-sectional studies without control of immediately preceding exposures or careful concurrent, blind testing of controls. Elevated immunoglobulin levels have been reported (4,24,25). Antichemical (e.g., formaldehyde) antibodies have been reported (26-28), as have elevated levels of autoantibodies (29). Changes in lymphocyte subsets have been reported (25-30). The preliminary description of T-cell subset abnormalities reported by Kipen et al. (25), have not been confirmed with testing of increased numbers of patients and inclusion of healthy controls (31). Elevated frequencies of activated lymphocytes are also described (27-29). Terr published on a case series of 50 worker's compensation patients and reported no abnormality of immunoglobulin, B-cell, and T-cell subset levels (13). Pathologic inflammatory changes in the nose have also been described (32),

and neurogenic inflammatory processes in the nose have been proposed as a pathogenic mechanism for MCS (33). Simon et al. (15) published the one carefully controlled and laboratory blinded case comparison study of subjects with chemical sensitivity (Table 8). Compared to subjects with musculoskeletal problems, tests for four autoantibodies, B-cells, and T-cell subsets showed no significant differences between the two groups. Tests for one autoantibody and two tests of immune cell activation (TA1 cell percentage and interleukin-1 [IL-1] generation) showed higher levels in the musculoskeletal group. Many values for individuals in both groups were abnormal according to laboratory reference ranges. Subsequent correspondence criticized the reported methods for both the antibody determinations and the determination of lymphocyte markers (34). Subsequently, the authors of this negative study disclosed that on a limited number of split samples, the reliability of the laboratory was little better than chance (35). It appears that the methods used in this study were similar to methods used in many of the positive studies referenced above. Thus, while immunologic abnormalities have been reported in chemically sensitive individuals, they have not been rigorously confirmed. Methodologic issues with respect to subject and control selection, laboratory blinding, and technique cloud our ability to be confident about the presence or absence of immunologic abnormalities in chemically sensitive individuals. Even if the types of immunologic changes reported above were confirmed, their role in advancing understanding of the origin or mechanisms of chemical sensitivity symptoms is not clear. The role of a psychoneuroimmunologic approach, including experimental paradigms for understanding the interactions among behavior, symptoms, and immunity, particularly with respect to controlled challenge testing, awaits explication.

## Summary and Conclusions

Controversy has surrounded the process for selecting or distinguishing patients who

**Table 8.** Comparison of immunologic studies in patients with multiple chemical sensitivity and controls with musculoskeletal injury.

Immunologic study	Cases (n = 41)	Controls (n = 34)	95% CI <sup>a</sup> for difference	p-Value
Positive test for autoantibodies, n (%)				
Antismooth muscle	20 (49)	16 (47)	(-0.22 to 0.24)	>0.2
Antiparietal cell	4 (10)	4 (12)	(-0.16 to 0.12)	>0.2
Antibrush border	5 (12)	11 (32)	(-0.02 to -0.40)	0.03
Antimitochondria	1 (2)	0 (0)	(-0.06 to 0.02)	>0.2
Antinuclear	4 (10)	2 (6)	(-0.04 to 0.22)	>0.2
Any positive	26 (63)	23 (68)	(-0.28 to 0.14)	>0.2
Cellular studies, ± SD				
Lymphocyte count, × 10 <sup>3</sup> /liter	2580 (± 546)	2450 (± 778)	(-171 to 431)	>0.2
B-cells, % (± SD)	6.4 (± 4.1)	7.4 (± 6.3)	(-1.4 to 3.8)	>0.2
T-cells, % (± SD)	69.8 (± 9.7)	67.4 (± 7.9)	(-1.6 to 6.4)	>0.2
CD4 <sup>+</sup> helper cells, % (± SD)	49.4 (± 9.2)	46.1 (± 7.1)	(-0.5 to 7.1)	0.1
CD8 <sup>+</sup> suppressor cells, % (± SD)	23.2 (± 7.7)	22.5 (± 7.4)	(-2.8 to 4.2)	>0.2
Interleukin-2 <sup>+</sup> cells, % (± SD)	2.1 (± 2.0)	2.1 (± 2.2)	NA <sup>b</sup>	>0.2 <sup>b</sup>
TA1 <sup>+</sup> cells, % (± SD)	6.5 (± 5.5)	13.0 (± 10.4)	NA <sup>b</sup>	0.008 <sup>b</sup>
Interleukin-1 generation	3.94 (± 5.02)	7.72 (± 6.09)	NA <sup>b</sup>	0.003 <sup>b</sup>

<sup>a</sup>Confidence Interval given in same units as original measure (proportions for serologic measures, percentages for lymphocyte subsets). <sup>b</sup>Skewed distribution requires use of Eilcoxon test; confidence interval not calculated. [From Simon et al. (15)].

have chemical sensitivity. That is, investigators and clinicians such as Rea (36) and Ross (37) include patients with diverse medical conditions as among those suffering from chemical sensitivities. Thus, their patient groups are highly heterogeneous while more recent investigators, using Cullen's definition (7), have attempted to reduce this heterogeneity by excluding other medical illnesses (10,15,38). Understanding the characteristics of the subjects under study is crucial to understanding the phenomenon of chemical sensitivity. Therefore, in future studies investigators may want to include patients with other diagnoses; subjects should be stratified by diagnostic category and analyzed distinctly from subjects whose primary clinical characteristic is sensitivity to low-level chemical exposure. Cross-sectional comparisons of MCS subjects have not revealed any consistent cognitive or immunologic pathology among patients whose primary clinical characterization is chemical sensitivity. Even among this potentially more homogeneous group, however, subjects suffer from a range of recognized psychiatric disorders, including depression and

anxiety. In fact, the most consistent finding among studies to date is that of a higher rate of any psychiatric disorder. Since no prospective studies have yet been undertaken, causality cannot be implied from these findings. Case definitions such as the one suggested by Cullen (7) may offer a false sense of homogeneity among patients. That is, at this stage of our understanding, it remains important to look carefully at individual data from subjects, since they may tell us more about the manifestations of this disorder than group comparisons when the groups are by necessity poorly defined. Finally, the crucial point that has yet to be addressed is the relationship between low-level chemical exposures and symptoms/objective illness reported by chemically sensitive patients. Whatever the causality, demonstrating a relationship between chemical exposure at the levels reported clinically and symptoms in a carefully defined set of patients is a necessary first step in determining whether chemical sensitivity represents an illness that requires a new model such as that described by Miller (39).

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