Profile of Patients with Chemical Injury and Sensitivity

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Patients reporting sensitivity to multiple chemicals at levels usually tolerated by the healthy population were administered standardized questionnaires to evaluate their symptoms and the exposures that aggravated these symptoms. Many patients were referred for medical tests. It is thought that patients with chemical sensitivity have organ abnormalities involving the liver, nervous system (brain, including limbic, peripheral, autonomic), immune system, and porphyrin metabolism, probably reflecting chemical injury to these systems. Laboratory results are not consistent with a psychologic origin of chemical sensitivity. Substantial overlap between chemical sensitivity, fibromyalgia, and chronic fatigue syndrome exists: the latter two conditions often involve chemical sensitivity and may even be the same disorder. Other disorders commonly seen in chemical sensitivity patients include headache (often migraine), chronic fatigue, musculoskeletal aching, chronic respiratory inflammation (rhinitis, sinusitis, laryngitis, asthma), attention deficit, and hyperactivity (affected younger children). Less common disorders include tremor, seizures, and mitral valve prolapse. Patients with these overlapping disorders should be evaluated for chemical sensitivity and excluded from control groups in future research. Agents whose exposures are associated with symptoms and suspected of causing onset of chemical sensitivity with chronic illness include gasoline, kerosene, natural gas, pesticides (especially chlordane and chlorpyrifos), solvents, new carpet and other renovation materials, adhesives/glues, fiberglass, carbonless copy paper, fabric softener, formaldehyde and glutaraldehyde, carpet shampoos (lauryl sulfate) and other cleaning agents, isocyanates, combustion products (poorly vented gas heaters, overheated batteries), and medications (dinitrochlorobenzene for warts, intranasally packed neosynephrine, prolonged antibiotics, and general anesthesia with petrochemicals). Multiple mechanisms of chemical injury that magnify response to exposures in chemically sensitive patients can include neurogenic inflammation (respiratory, gastrointestinal, genitourinary), kindling and time-dependent sensitization (neurologic), impaired porphyrin metabolism (multiple organs), and immune activation. — Environ Health Perspect 105(Suppl 2):417–436 (1997)

Key words: multiple chemical sensitivity, fibromyalgia, chronic fatigue syndrome, neuropsychological tests, toxic encephalopathy, autoimmunity (or autoimmune diseases), immune activation, acquired disorders of porphyrin metabolism (or porphyria), chemically induced, pesticides, solvents, respiratory inflammation

Introduction

The study of medicine "begins with the patient, continues with the patient and ends ... with the patient," according to William Osler (*1*). Exposure to chemicals, particularly petrochemicals and combustion products, has been associated in the literature with a variety of alterations in bodily functions. Porphyrin disturbances of various types following chemical and heavy metal exposures were reported by several authors in a special conference on chemically induced porphyrinopathies sponsored by the New York Academy of Sciences (*2*). Abnormally elevated levels of urinary coproporphyrins were reported in several papers, but other fecal and urinary porphyrins could be increased as well. Specific types of heavy metal and petrochemical exposures seem to cause specific patterns of porphyrin disturbance in rats (*3*). Chlorinated benzenes can induce porphyria in rats (*4*), and small exposures (such as swallowed mouthwash) can aggravate congenital porphyria (*5*). Immune disturbances following chemical exposure have been reported by several authors. In the following immune references, patients were studied only after probable causal exposure and the results were compared to those of laboratory normals. Impaired mitogenesis has been noted after exposure to chlordane (*6*) and isocyanates (*7*). A higher number of helper cells have been described in workers exposed to solvents (*8*) and isocyanates (*7*), and in persons consuming chlorinated solvents in drinking water (*9*). A greater number of immune complexes are reported with vinyl chloride exposure, and scleroderma has been noted after aromatic or chlorinated solvent exposure (*10*). Immune activation with higher levels of TA1/CD26 has been reported with isocyanates (*7*), formaldehyde (*11*), formaldehyde with aliphatic amines (*12*), silicone (*13*), chlordane and chlorpyrifos (*14*), and sick-building exposures (*15*).

Higher levels of abnormalities in various autoantibodies are described after a wide variety of chemical exposures, including chlordane (*6*), solvents (*16,17*), chlorinated solvents (*9*), polychlorinated biphenyls and polybrominated biphenyls (*18*), organochlorine, organophosphate and other pesticides (*19*), formaldehyde and aliphatic amines (*12*), silicone (*13,20*), chlordane (*14*), chlorpyrifos (*14*), malathion (*14*), and formaldehyde (*11*). A greater number of chemical-specific antibodies has been noted after exposure to building materials in remodeling (*21*). Suppression of mitogenesis (*22*) and natural killer cell (NK) function (*23*) has been described following anesthesia induced by petrochemical agents. Reduced NK function in multiple chemical sensitivity (MCS) patients also has been reported by Heuser (*24*).

Neurologic effects long have been associated with exposure to petrochemicals. Solvent exposure is associated with autonomic dysfunction (*25*), neurocognitive impairment (*26,27*), vestibular abnormalities (*28*), and impaired hearing (*29*). In a study of the effects of solvents on 15

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Abbreviations used: AAL, Antibody Assay Laboratory; ALA-D, aminolevulenic acid dehydratase; CD, cluster of differentiation; CFS, chronic fatigue syndrome; conA, concanavalin A; CpgO, coproporhyrinogen oxidase;; EEGs, electroencephalograms; ISL, Immunosciences Laboratory; MCS, multiple chemical sensitivity; NK, natural killer cell; PbgD, porphobilinogen deaminase; PHA, phytohemagglutinin; SPECT, single photon emission computed tomography; WAIS-R, Wechsler adult intelligence scale–revised.

industrial painters (*30*), impairment was observed on a variety of neuropsychological measures. The Halstead-Reitan Battery was administered and impairment was found on the Impairment Index, Trails A, Digit Symbol, Seashore Rhythm and Speech Sounds-Perception Tests. In addition, subjects reported personality change and decreased memory.

Neurological abnormalities in a group of organophosphate-exposed subjects were described using the Halstead-Reitan Battery (*31*). Visual retention, memory dysfunction, and constructional deficits were reported (*32*).

Studies on chlorinated hydrocarbon solvents have also shown adverse effects. Trichloroethylene in low concentrations and for relatively brief times can lead to significant and prolonged impairment (*33*). Psychomotor speed and memory were two of the areas most affected, with the memory impairments characterized by storage and retrieval difficulties.

Neuropsychological changes have been found among community residents living in a supposedly benign environment such as areas adjacent to a wood-treating plant (*34*). Of the 34 subjects tested, more than 40% had sensory impairments, 86% had motor or psychomotor speed problems, and 72% had concentration difficulties. Disturbed autonomic function has been reported with chemical sensitivity (*35*), and abnormal neurocognitive function with chemical sensitivity/cacosmia (*36*).

Chemical sensitivity has been reported in the literature following exposure to chlordane (*14*), chlorpyrifos (*37*), pesticides (*38*), formaldehyde (*39*), tight or sick buildings (*15*), and organophosphates and solvents (*40*). These chemicals are not structurally related, although all may form free radicals and cause tissue damage.

A wide range of neurologic abnormalities [single photon emission computed tomography (SPECT), nerve conduction, electro encephalograms (EEGs), evoked potentials, neurocognitive] have been reported in chemically sensitive patients (*41–43*). Since depression and mood swings can occur with solvent/hydrocarbon exposures and with porphyrin disturbances, these are not in themselves evidence of a psychologic etiology of MCS (*40*). These and other studies strongly suggest that chemical sensitivity is a physiologic not a psychologic disorder (*35,36,44*).

A 1994 study found that 67% of patients with fibromyalgia and the same percentage with chronic fatigue syndrome (CFS) reported that their symptoms worsened on exposure to gas, paint, or solvent fumes, and 46 to 64% of these groups reported sensitivities to three other categories of common chemical exposures (*45*). Fibromyalgia patients have shown reduced current perception threshold (*46*) and T-cell changes (*47*). Chronic fatigue syndrome patients often meet criteria for fibromyalgia (*48*) and have impaired NK function, increased TA1/CD26, altered CD8, impaired mitogenesis (*49,50*), and vestibular and other neurologic abnormalities (*51*). Both chemical sensitivity (*52*) and chronic fatigue syndrome (*53*) have been postulated to involve limbic encephalopathy.

We describe medical findings on history, physical exam, and laboratory testing for patients who, in the wake of chemical exposure, developed chronic illness with multi-systemic symptoms exacerbated by exposures to multiple different chemicals at levels usually tolerated by most healthy members of the general population and previously tolerated by the patient.

Methods

Ziem's medical practice has been evaluating and caring for patients with MCS accompanied by chronic illness for many years, assisting them with environmental controls to reduce exposure and addressing clinical issues related to their exposure. Typically, an initial evaluation requires 1.5 to 2 hr for medical and exposure history, physical exam, evaluation of environmental aggravating factors, recommendations for environmental controls, and otherwise addressing clinical problems. Follow-up evaluations usually require 1 to 1.5 hr. This time-intensive approach to the evaluation of chemically injured patients contrasts with what we consider to be a too-cursory assessment prevalent among many industrial and academic professionals. We do not believe it is possible to evaluate and manage these disorders adequately in the 10 to 30 min usually allotted to such patients.

In the late 1980s, Ziem introduced a standardized questionnaire for initial patient assessment to evaluate the types of symptoms present, possible organ systems involved, and the types of chemical exposures perceived by these patients to be aggravating their symptoms. The full questionnaire is 16 pages long with 46 detailed questions. Reported here are the responses to questions 14 and 6 (Appendices 1 and 2) from 91 chemically sensitive patients whose first visit occurred after the introduction of the questionnaire. These two questions originally were developed by Dr. Ann Davidoff of the Johns Hopkins School of Hygiene and Public Health as part of a research project on chemical sensitivity (*54*).

Patients responding to the questionnaire came from many states from the eastern region of the United States, with most coming from the mid-Atlantic area. Most were referred by physicians not specializing in occupational medicine or toxic substances. Some were referred by patient support groups, friends, or relatives, and a few were legal referrals (although we have no data on the actual number in each category). Most but not all patients were well before the onset of their MCS. Former psychiatric diagnoses and treatment were unusual rather than typical.

In following these patients over time, Ziem's clinical impression is that patient responses to these two questions seem to correlate well with the clinical severity of their symptoms: sicker patients appear to have more frequent symptoms and to be affected by more exposures. However, it was not possible for this presentation to confirm this clinical impression by comparing response rates to exposures with clinical outcomes. This would be useful for future clinical studies. Symptom frequency can also be studied as an indicator of clinical severity.

These patients filled out the questionnaires at or shortly before their first visit. Some had been using some environmental controls; others had not. Many but not all patients were aware of chemical sensitivity as a potential problem for them. To assess the frequency of 51 different symptoms commonly associated with MCS, patients were asked in question 14 to describe whether these symptoms occur daily to almost daily, several times a week, once a week, several times per month, once per month or less, rarely, if ever, or not sure. In the analysis below, daily or almost daily responses are combined with several times a week or more responses to obtain a total figure for frequent symptoms.

All patients reporting increased sensitivity to chemicals accompanied by chronic illness were included in this analysis. They typically had frequent recurring or chronic symptoms in more than one organ system for over 6 months before completing the questionnaire. For some items in question 14, responses were only available for 89 or 90 patients: the bar graph in Figure 1 shows the number of patients (n) answering for each question. Outcomes are reported as percentages of the total answering each

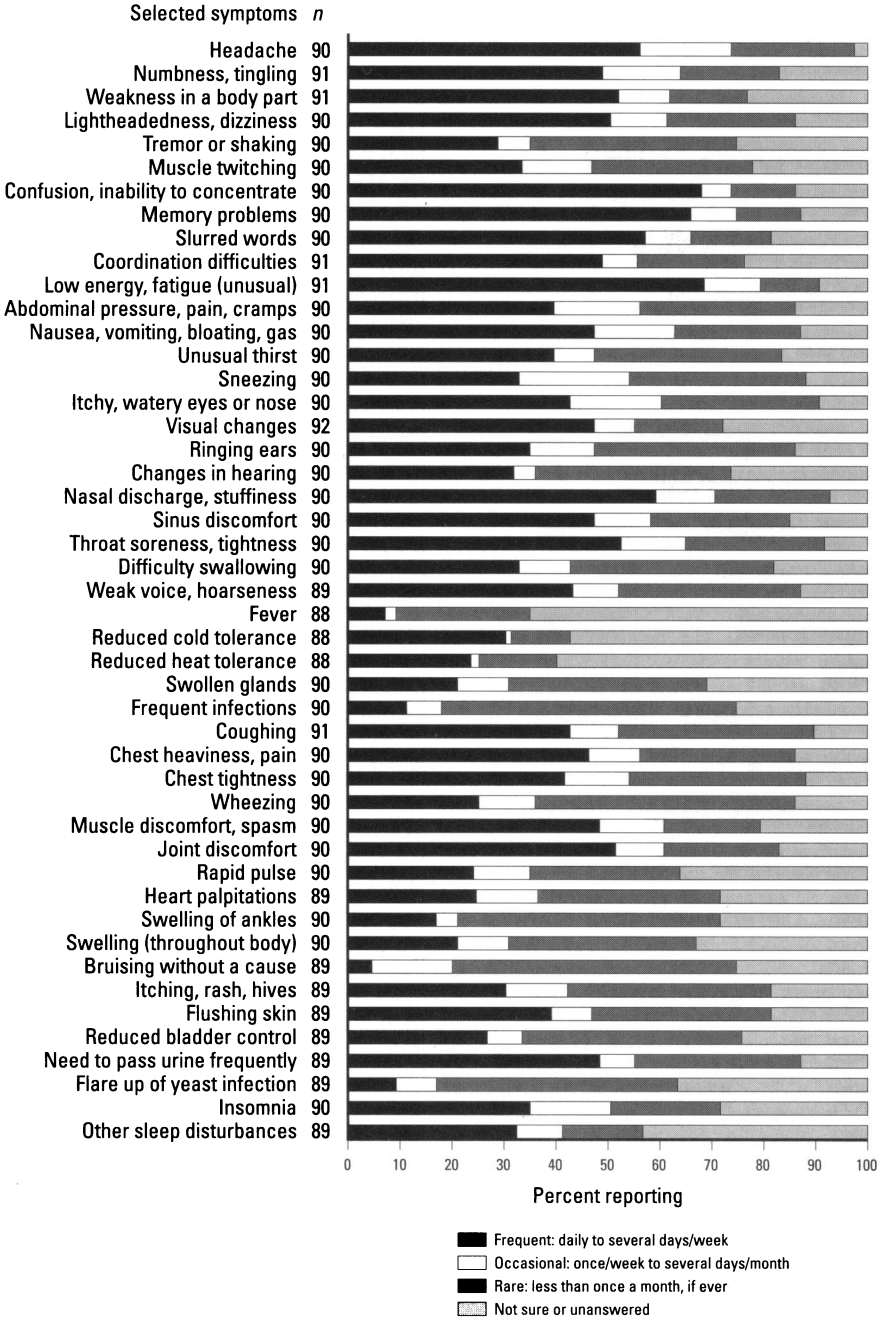

Figure 1. Relative frequency of select symptoms as reported by Ziem's MCS patients.

item. The bar for each symptom displays separately symptoms occurring daily to several times a week (combined totals from the first two columns from Appendix 1) and once a week to several times a month (combined totals from columns 3 and 4 from Appendix 1). These percents are then added to show the total percent with symptoms several times a month or more (this percent figure is shown to the right of first bar for each symptom). As an example, 57% of patients had headache daily to several times a week and 18% had headache weekly to several times a month—a total of 75% of patients experiencing headache several times a month or more.

Question 6 of the questionnaire, taken from the Davidoff study of MCS patients conducted at Johns Hopkins (*54*), has two parts. In the first part, patients were asked if they thought they would be sick following a 20-min or a 4-hr carefully defined exposure to a variety of common petrochemicals and irritants (Figure 2). In the second part of the questionnaire, they were asked if their symptoms would be exacerbated by a different set of briefer exposures (Figure 3).

Laboratory testing was recommended for most patients, more so in recent years as knowledge of MCS-related abnormalities grew. A few patients have had EEG, quantitative electroencephalogram, nerve conduction studies, SPECT scans, etc., but these data are not reviewed here because of the small numbers involved [and because these abnormalities in MCS patients have been reported elsewhere (*42*)]. Also, for all testing, financial constraints were often operative: disabled patients without adequate insurance were less able to afford testing. As a result, it is possible that tested patients were less severely affected than untested patients.

Immune testing was recommended for nearly all patients after the practice reviewed immune results in the late 1980s on six chlordane-exposed patients all showing increased activation and/or autoimmunity to evaluate whether the symptom of sensitivity to chemicals was accompanied by objective immune changes. Once it was determined that neurocognitive changes could be documented in MCS patients, those patients who described frequent impairment in thinking, concentration, and/or memory were referred for neurocognitive evaluation. Patients were referred for porphyrin testing beginning in 1995 if they had a history of brown or red urine not due to blood, or two or more porphyrialike symptoms such as abdominal pain with exposure, skin symptoms with sunlight, symptoms with fasting or skipping meals, or skin symptoms with exposure to metals. Thus, testing followed the usual clinical pattern of evaluation of patients more likely to be abnormal rather than a research pattern of testing every patient.

The practice has extensive data on immune testing, including testing of autoimmune parameters, immune activation, and T-cell subsets. The different normal values for CD4 and CD26 for the two different labs probably result largely from only one [Immunosciences Laboratory (ISL), Beverly Hills, California] of the two labs using flow cytometry. These immune tests were first done using the Antibody Assay Laboratory (AAL) in Santa Ana, California (for 68 patients) and, more recently, the ISL (for 23 patients). The latter

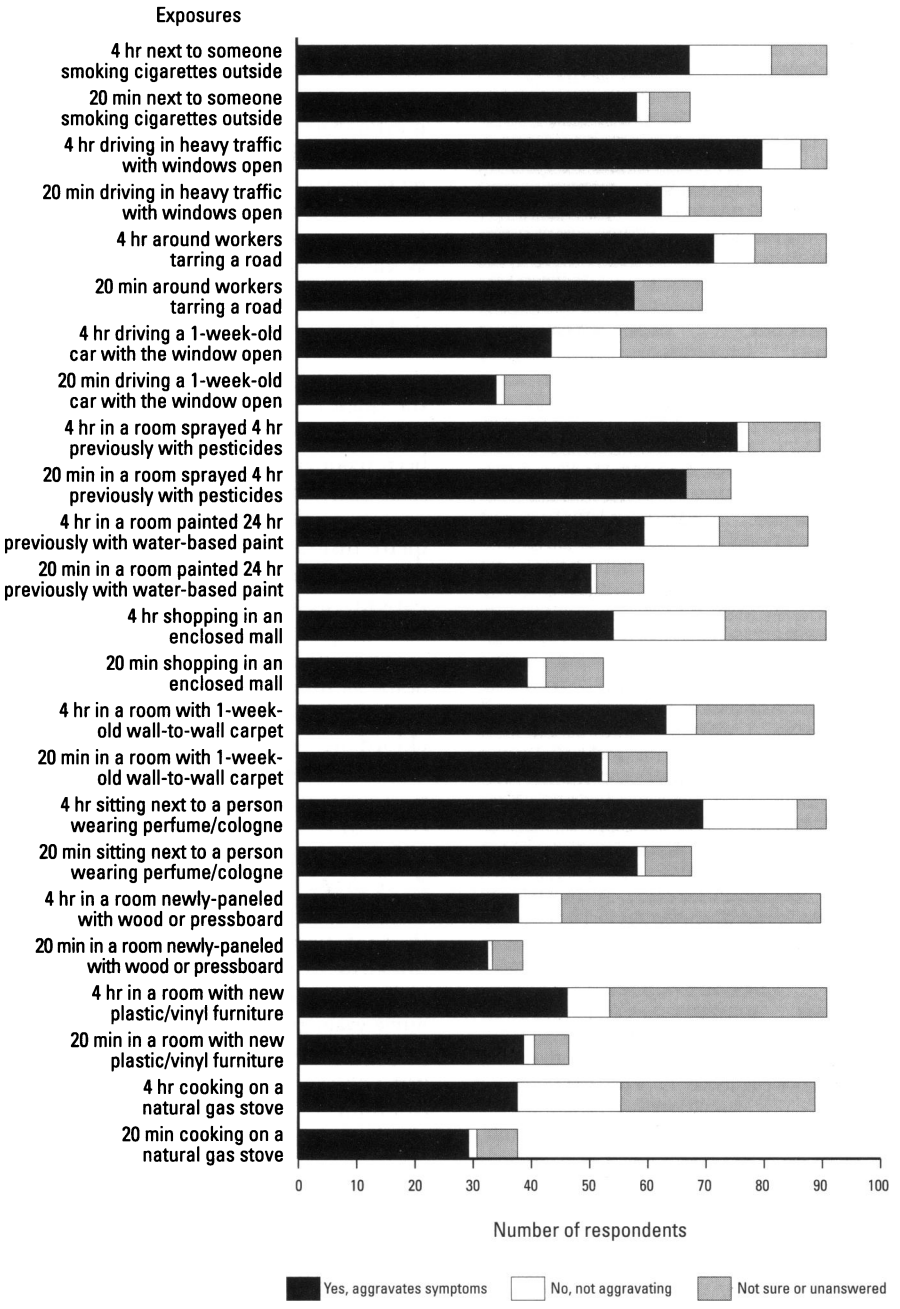

Figure 2. Comparison of sensitivity to select exposures after 4 hr and 20 min as reported by Ziem's MCS patients.

laboratory also included tests of T- and B-cell function, which were not requested of the AAL.

Beginning in 1995, MCS patients with neurological and/or cutaneous symptoms suggesting porphyrin disorders have been screened for the various biomarkers of those conditions that may be detected in blood, urine, and stool. Samples were collected locally by independent laboratories and sent for analysis (via overnight delivery) to the Mayo Medical Laboratories in Rochester, Minnesota. Mayo was selected both because of its excellent reputation and because it offers more porphyrin-related tests than any other commercial laboratory in the United States. A full panel includes tests for five of the porphyrin-related enzymes involved in the heme synthesis pathway [aminolevulenic acid dehydratase (ALA-D), porphobilinogen deaminase, also known as uroporphyrinogen I synthase, uroporphyrinogen III cosynthase, uroporphyrinogen decarboxylase, and coproporphyrinogen oxidase], δ-aminolevulinic acid in urine, porphobilinogen in urine, quantitative urinary porphyrins, and fractionated fecal porphyrins. Results are presented for six MCS patients from Ziem's practice who have undergone all these tests and eight others who have undergone most of them (Table 1). Data on the three other patients screened are not included, as they each had undergone only one or two of the recommended tests, although two patients showed some abnormalities—one with decreased coproporhyrinogen oxidase (but no urine or fecal testing) and one with increased urinary coproporphyrins (but no blood or stool testing). In terms of both symptoms and history, the patients tested for porphyrin disorders were fairly representative of all chemically sensitive patients in this medical practice and none were known to have any other disorder associated in the literature with abnormal porphyrin metabolism (such as lead poisoning, hepatitis C, or liver cancer).

Patients diagnosed with MCS and describing difficulty with thinking, concentration, and/or memory were referred for neurocognitive testing. Those who live near Baltimore, Maryland, were referred to Dr. James McTamney, a clinical psychologist. As of September 1995, 13 patients had completed testing with Dr. McTamney. Patients in other geographic areas sometimes went elsewhere for testing, but because testing approaches and the tests used were different, these patients' data are not analyzed here. Dr. McTamney's evaluation included the Wechsler Adult Intelligence Scale–Revised (WAIS-R) (Table 2) and the Halstead-Reitan Battery (Table 3). The Halstead-Reitan Neuropsychological Battery is generally conceded to be a reliable psychological means of identifying patients with brain damage. It is an individually administered battery composed of the following tests: the Category test, the Tactile Performance test, the Seashore Rhythm test, the Speech Sounds Perception test, the Finger Oscillation test, and Trails A and B.

The Category test is a complex test of new problem solving, judgment, abstract reasoning, concept formation, mental flexibility, and mental efficiency. It requires a number of higher order functions such as the ability to note similarities and differences among stimuli and to formulate hypotheses regarding the principle that determines the correct answer. It is also a test of learning ability utilizing nonverbal

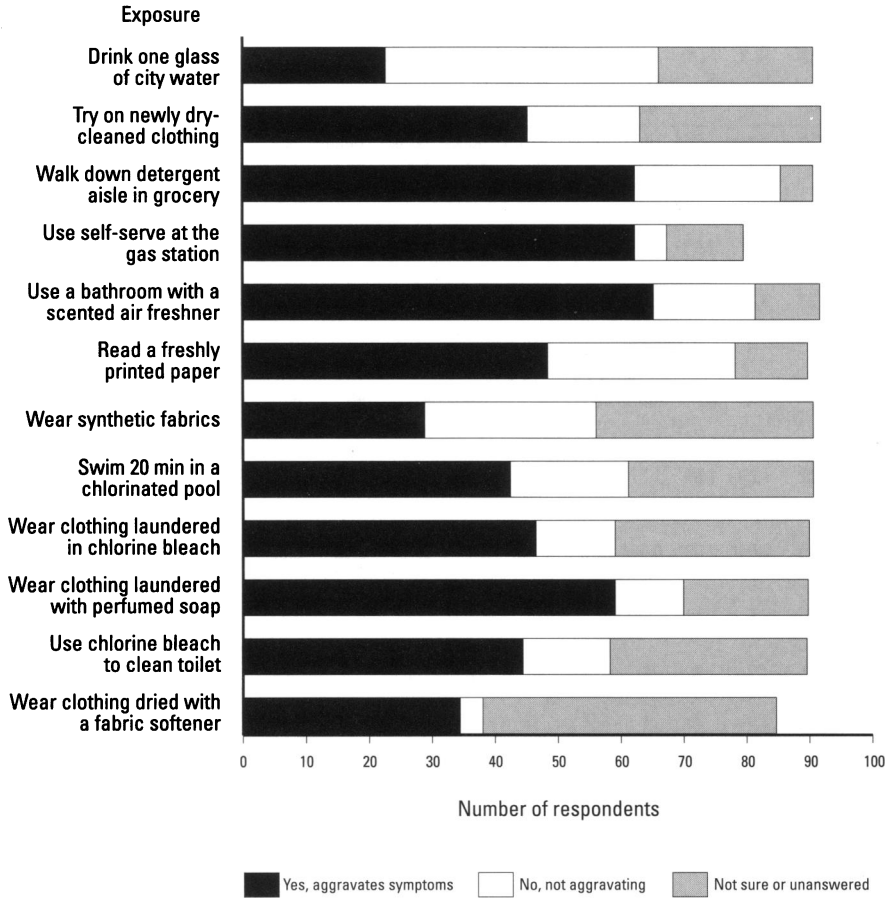

Figure 3. Sensitivity to other select brief exposures as reported by Ziem's MCS patients.

material. Finally, there is a memory component to the test that requires the person to remember which principle was correct in determining the answer to an individual item. This requires a longer recall of previously learned correct responses.

The Tactile Performance test is a complex test requiring the individual to sustain adequate strength and speed of movement. It also requires the tactile perception and the ability to form a visual map of the board. The person, while blindfolded, must place ten blocks with the dominant hand on the first trial and then ten blocks with the nondominant hand on the second trial. On the third trial, the individual is allowed to use both hands together. After the trials are completed, the blindfold is removed and the person asked to draw the blocks approximating their size, shape, and relationships to one another while the blocks are out of sight.

The Seashore Rhythm test requires the individual to listen to 30 pairs of rhythmic beats from a tape recording and to select the proper response on an answer sheet as to whether the two tones in each pair are the same or different. The test requires the individual to discriminate between different patterns of nonverbal sounds while maintaining attention and concentration throughout the test.

On the Speech Sounds Perception test, the individual has a sheet of paper on which 60 groups of four nonsense words are listed. The individual must underline the correct response after hearing it on the audio tape recording.

On the Finger Oscillation test, the individual is required to tap as rapidly as possible with the index finger on a small lever attached to a mechanical counter. The person is given five consecutive 10-sec trials with the preferred hand and then five consecutive trials with the nonpreferred hand. The scores in this test are the average number of taps in a 10-sec period for each hand. The cutoff point indicating impairment would be less than 50 taps per hand on average.

Trails A and B do not contribute to the Halstead Impairment index but are considered a part of the Halstead-Reitan Battery. On the Trails A, the person is required to connect 24 numbered circles distributed in a random pattern while being timed for the performance. On Trails B, the person is required to connect circles numbered 1 through 13 and letters A through L alternating from number to letter in sequence.

The overall impairment index is calculated as the number of subtests within the impaired range divided by the overall number of subtests taken.

WAIS-R is a scale of an individually administered composite of tests in battery format. For all but the most severely impaired adults, a WAIS-R battery constitutes a substantial portion of the test framework of the neuropsychological examination. Eleven different subtests make up the WAIS-R battery. Six of the subtests are classified as verbal tests: Information, Comprehension, Arithmetic, Similarities, Digit Span, and Vocabulary. Five are termed performance tests and measure nonverbal/visuospatial factors. The tests are Digit Symbol, Picture Completion, Block Design, Picture Arrangement and Object Assembly.

We invite independent scientific review of our actual clinical data to further understanding of these patients' chemical injury and chemical sensitivity.

Results

The vast majority of these patients reported some symptoms occurring daily to almost daily (Figure 1). Symptoms that could reflect respiratory responses to irritant exposures were frequent (several times a week or more): patients indicated nasal symptoms (60%), sinus discomfort (48%), throat discomfort (53%), weak voice/hoarseness (44%), chest tightness (42%), and wheezing (25%). The higher percentages of patients reporting nose and throat symptoms suggest that irritant effects may be greatest in the upper respiratory tract—areas that first encounter respiratory irritants (nose, throat, etc.)—and less as these irritants move down the respiratory tract. This is consistent with partial irritant removal as the inhaled air moves down the respiratory tract.

Frequent symptoms that suggest neurologic involvement were reported by many patients: tremor or shaking (29%), muscle twitching (33%), memory problems (67%), slurred words/difficulty finding words (58%), coordination difficulties

Table 1. Disorders of porphyrin metabolism in 14 multiple chemical sensitivity patients tested by Mayo Medical Laboratories.[a]

Selected tests performed	Mayo Lab normal range	Mayo Lab abnormal range	Pt 1 F 50y	Pt 2 F 42y	Pt 3 M 44y	Pt 4 F 53y	Pt 5 F 42y	Pt 6 F 49y	Pt 7 M 52y	Pt 8 F 49y	Pt 9 F 38y	Pt 10 M 42y	Pt 11 M 51y	Pt 12 M 11y	Pt 13 M 47y	Pt 14 M 55y	Outside norm, %
Probable causal exposure			Solv	B impl	Phen	OPO4	Unk	Renov	Renov	Renov	Tce&d	Chlord	Unk	Unk	Vocs	Cl agt	
δ-Aminolevulinic acid in urine (marker of ALA synthase activity), mg/dl	1.5–7.5 (≥ 6 yr)	>7.5	NA	NA	NA	NA	2.4	NA	NA	2.5	1.7	26.4*	3.8	1.7	2.2	1.2	13
ALA-D in erythrocytes, nmol/sec/liter	≥4.0	<3.5	3.9*	4.0	3.6*	2.8*	4.6	3.2*	2.7*	5.3	7.2	4.7	2.7*	4.2	3.4*	5.0	50
Porphobilinogen deaminase in erythrocytes (also known as uroporphyrinogen I synthase), nmol/sec/liter	≥7.0	<6.0	7.0	6.2*	6.3*	4.4*	6.9*	4.7*	4.1*	8.8	11.1	7.1	4.1*	7.6	8.6	8.0	50
Uroporphyrinogen III cosynthase in erythrocytes, relative units of activity	≥40	≤10	91	83	NA	84	88	88	88	NA	91	86	88	91	86	68	0
Uroporphyrinogen decarboxylase in erythrocytes, relative units of activity	1.00–3.00	<0.80	1.53	1.22	1.09	1.04	1.51	2.58	1.06	1.52	1.43	1.43	1.06	2.81	2.02	1.23	0
Coproporphyrinogen oxidase in erythrocytes (reticulocytes), relative units of activity	0.10–0.30	<0.06	0.14	0.10	0.04*	0.09*	0.08*	0.10	0.03*	0.11	0.12	0.05*	0.03*	0.07*	0.08*	0.03*	64
Porphyrins in urine (quantitative), mg/24 hr																	
Uroporphyrins	≤46 M, 22 F	>46 M, 22 F	8	23*	23	6	6	9	13	8	5	7	13	NA	7	7	8
Heptacarboxylporphyrins	≤13 M, 9 F	>13 M, 9 F	2	<3	6	2	1	2	3	1	<1	2	3	NA	4	2	0
Hexacarboxylporphyrins	≤5 M, 4 F	>5 M, 4 F	<1	<3	3	1	<1	<1	2	3	<1	<1	2	NA	1	<1	0
Pentacarboxylporphyrins	≤4 M, 3 F	>4 M, 3 F	2	<3	7*	5*	3	<1	4	2	<1	6*	4	NA	<1	2	23
Copro or tetracarboxylporphyrins	≤96 M, 60 F	>96 M, 60 F	59	89*	163*	112*	62*	84*	112*	49	28	73	112*	NA	89	59	54
Porphobilinogen in urine, mg/24 hr	≤1.5	>2.0	1.7*	NA	NA	0.4	1.2	0.1	1.1	0.8	0.8	<0.1	1.1	NA	1.1	0.7	9
Porphyrins in feces (fractionation), μg/24 hr																	
Coproporphyrins	≤200	>200	71	NA	NA	IS	397*	227*	90	170	40	111	90	NA	129	166	20
Uroporphyrins	=1500	>1500	20	NA	NA	IS	59*	25	23	115	18	21	23	11	30	146	9
Protoporphyrins	≤1000	>1000	175	NA	NA	IS	486*	170	189	1206	87	288	189	175	286	1002*	18

[a]These are not necessarily the same patients as in Tables 2 and 3. Patients 12, 13 and 14 were added after Ziem's presentation at NIEHS Conference on Experimental Approaches to MCS: Profile of Patient Characteristics: Chemical Injury and Chemical Sensitivity, 20 September 1995, Princeton, New Jersey. Abbreviations: Pt, patient; F, female; M, male; y, years of age; B impl, breast implant; Chlord, chlordane; Cl agt, cleaning agents; IS, insufficient sample; NA, not available; OPO4, organophosphate pesticide; Phen, phenol; Renov, renovation (all U.S. EPA headquarters buildings); Solv, solvents; Tce&d, trichlorethylene and Dursban; Unk, unknown; Vocs, volatile organic compounds (offgassing from new computers). *, a result outside the Mayo reference range of normal.

Table 2. WAIS-R neuropsychological evaluation of 13 multiple chemical sensitivity patients.[a]

Patient ID	Information	Digit scan	Vocabulary	Arithmetic	Comprehension	Similarities	Picture completion	Picture arrangement	Block design	Object assembly	Digit symbol	IQ, verbal/performance
1	7	8	10	8	9	12	7	8	9	9	6	104/86*
2	12	3	15	9	14	11	3	10	7	7	7	106/88*
3	9	12	10	11	8	8	11	8	9	12	11	98/106
4	8	6	8	6	8	8	7	7	10	6	9	86/90
5	8	9	6	7	8	6	5	6	6	5	9	87/85
6	10	13	11	15	12	8	12	8	10	8	8	112/105
7	12	4	11	5	11	13	5	6	7	7	2	96/78*
8	8	8	9	8	9	9	9	8	8	8	9	92/94
9	15	8	12	14	14	10	4	5	7	7	4	118/85*
10	7	8	12	5	14	9	6	7	7	10	6	95/87
11	12	13	15	8	15	13	10	10	9	6	11	120/105*
12	16	12	16	15	12	15	11	15	14	12	11	131/130
13	12	12	16	13	14	13	10	7	8	8	6	125/100*
											Percent IQ verbal/performance abnormal >	6/13 = 46%

[a]Same patients as in Table 3. *, significant difference between verbal and performance IQ scores.

Table 3. Halstead-Reitan neuropsychological evaluation of 13 multiple chemical sensitivity patients.[a]

Patient	Tactile performance test									Finger oscillation		Trails		Impairment
ID	CAT	TT	DOM	NDOM	BH	MEM	LOC	Rhy	Ssds	DOM	NDOM	A	B	index
1	63*	14′24″	4′11″ (25″)	7′18″* (44″)	2′55″ (18″)	7	4*	3	0	34*	30*	65″*	155″*	0.4
2	63*	18′05″*	8′08″ (48″)	5′39″ (34″)	4′18″ (26″)	8	2*	12*	4	21*	20*	60″*	152″*	0.7*
3	17	18′20″*	6′55″ (41″)	7′15″* (43″)	4′10″ (25″)	6	2*	5*	9*	49	51	18″	56″	0.5*
4	26	13′05″	4′35″ (28″)	4′30″ (27″)	4′00″ (24″)	5*	2*	2	10*	57	56	27″	82″	0.4
5	83*	16′08″*	5′58″ (36″)	5′45″ (35″)	4′25″ (27″)	4*	2*	8*	10*	23*	20*	66″*	120″*	1.0*
6	38	13′00″	7′57″ (48″)	2′59″ (18″)	2′04″ (12″)	7	5	9*	3	55	46	27″	72″	0.3
7	70*	27′58″*	14′01″ (84″)	10′01″ (60″)	3′56″ (39″)	7	4*	14*	27*	33*	28*	86″*	162″*	0.8*
8	71*	16′20″*	6′00″ (36″)	7′30″* (45″)	2′50″ (17″)	7	3*	5*	10*	44*	40*	35″	95″*	0.8*
9	108*	28′54″*	10′3″ (60″)	13′45″* (82″)	5′06″ (30″)	5*	3*	7*	8*	60	53	50″*	101″*	0.8*
10	90*	16′34″*	7′52″ (47″)	5′24″ (32″)	3′18″ (20″)	7	5	1	7	43*	40*	49″*	128″*	0.4
11	108*	13′56″	7′33″ (45″)	3′20″ (20″)	3′03″ (18″)	7	4*	0	4	50	43*	37″	56″	0.4
12	19	10′54″	4′26″ (27″)	3′54″ (23″)	2′34″ (15″)	8	4*	3	3	62	50	25″	37″	0.1
13	55*	17′52″*	5′07″ (31″)	8′33″ (51″)	4′12″ (25″)	8	2*	2	6	44*	43*	49″*	114″*	0.5*
% IMP	9/13 69	8/13 62	0/13 0	3/13 23	0/13 0	3/13 23	11/13 85	7/13 54	6/13 46	7/13 54	8/13 62	7/13 54	8/13 62	7/13 54

Abbreviations: % IMP, percent impaired among total tested; BH, time for both hands together; CAT, category test; DOM, time for dominant hand; LOC, location; MEM, memory; NDOM, time for nondominant hand; Rhy, rhythm (seashore); Ssds, speech sounds perceptions test; TT, total time. [a]Same patients as in Table 2. *, an impaired score.

(49%), and reduced bladder control (27%). The latter suggests possible involvement of the autonomic nervous system, as do some other frequently reported symptoms such as flushing skin (39%), rapid pulse (24%), palpitations (25%), reduced cold tolerance (31%), and reduced heat tolerance (24%). Based on patient exams and Holter monitoring, ectopic heartbeats appear more frequently during exposures and in sicker patients, but these data have not been analyzed in the aggregate. Mitral valve prolapse, a probable autonomic disorder, appeared to be unusually common in our chemically sensitive patients, possibly 10% or more, but this too has not been quantified in the aggregate. Murmurs seemed to subside with clinical improvement in some cases.

Symptoms of sensory organs were also reported to be frequent by a significant percentage of MCS patients: changes in hearing (32%), visual changes (48%), and ringing ears (36%). (Clinically, visual changes usually involve blurred vision with exposure.) Symptoms suggesting inflammation such as swollen glands, muscle discomfort/spasm, and joint discomfort also were commonly reported to be frequent by 21, 49, and 52% of patients, respectively. Frequent abdominal discomfort was experienced by 40%, consistent with abnormalities in porphyrin metabolism, as described below. Headache and unusual fatigue were frequent in 57 and 69% of patients, respectively. The 40% reporting frequent unusual thirst was an unexpected finding and may indicate endocrine changes in this group. The finding of significant musculoskeletal aching and fatigue among MCS patients is interesting in light of the overlap in symptomatology and clinical findings between MCS, fibromyalgia syndrome, and chronic fatigue syndrome (*45*).

In response to question 6 (Figure 2), more than two-thirds of the patients reported symptoms with exposure to combustion products such as passive cigarette smoke and vehicle exhaust and to many other frequently encountered indoor and outdoor petrochemical air pollutants (new carpets, pesticides, paint, scented products, etc.); half or more of the patients reported symptoms when exposed to other irritants such as detergents or chlorine. In this group of patients, the vast majority who reported symptoms with 4-hr exposures also experienced symptoms with only 20-min exposure. This has implications for reasonable accommodation: requiring daily commuting, work, or even brief meetings in newly carpeted, remodeled or recently pesticide-treated areas could aggravate symptoms in a significant proportion of persons with chemical sensitivity. It also suggests that many current products and practices involving chemicals (remodeling, cleaning, repairs, pesticide application, etc.) present frequent problems for these patients.

Ziem first encountered cellular immune abnormalities while evaluating a cluster of eight chlordane-exposed patients with chemical sensitivity in the late 1980s. She has checked for similar immune abnormalities in other chemically exposed patients

with chemical sensitivity, using the AAL for testing on the first 68 patients (Table 4).

Compared to lab normals, the majority of those tested by AAL had increased total CD26 (also known as TA1) cells, which is considered a marker of immune activation (*55*). Seventeen (25%) had increased CD4 (helper T lymphocytes). Only five had increased CD8 (suppresser T lymphocytes). NK (CD57) evaluations were done on only 15 patients but were reduced in number in 5. B lymphocyte (CD14) values are available for 57 patients; these were reduced in 18 (32%) and increased in 1 patient. Judgments of abnormal and normal ranges were made by the laboratory, but the raw data and the laboratory's normal reference ranges are provided for independent review.

Autoantibodies were evaluated and found to be present in increased titer in some cases: antimyelin (nervous system) autoantibodies and antismooth muscle (liver) in about half the patients, with antiparietal (stomach), antibrush border (kidney), antimitochondrial, and antinuclear in only a small number of patients. AAL considered myelin antibodies abnormal if titers were over 1.8; other autoantibodies were considered abnormal if titer levels were 1:20 or greater. Exact titer levels were not reported (by AAL) but may have provided additional information. Ziems's clinical impression is that as patients improved, some titers fell within the laboratory's normal range, but longitudinal data have not been quantified in aggregate. Titer levels facilitate comparison of changes in clinical status with increase or decline in titer levels. The striking proportion with autoantibodies against liver and nervous system tissue (about half the total patients tested for each) is consistent with neurologic effects and liver involvement, which is consistent with porphyrin disturbance.

Table 4 also lists the location, situation, and chemical(s) involved in each patient's presumed causal exposure when this could be determined. An exposure was considered causal for this purpose if: there were no symptoms of multiple chemical sensitivity accompanied by chronic illness before the exposure; significant symptoms occurred during or shortly after the exposure (within days); symptoms improved away from the exposure on at least two occasions; and symptoms recurred on reexposure on at least one occasion. For any particular products associated with causal exposures, the chemicals involved were identified whenever possible, usually from material safety data sheets.

Over half the patients listed in Table 4 were considered occupational in probable causal exposure: 23 in the private sector (OCP in Table 4) and 14 in government or the public sector (OCG). Many public-sector exposures appeared to involve tight buildings. Public sector reluctance to tackle the chemical sensitivity problem might be affected by a substantial number of compensation cases filed by public sector employees. School exposures accounted for eight cases, all involving pesticides, and primarily affected students. Home exposures involved over a fourth of the total cases seen by Ziem. Nearly a third of all cases were felt by Ziem to be caused by pesticide exposure.

After Simon raised questions about the reliability of AAL testing in April 1994—he said the results of split samples secretly submitted to the laboratory showed that "the reliability on most of their measures is no better than chance" (*56*)—Ziem arranged for subsequent immune function testing to be performed by the ISL. In this presentation of ISL data, both normal and abnormal results are shown but only for those particular tests done on more than half the patients (Table 5). The only ISL data excluded after analysis are those on MY, GP, SG, and AS neural autoantibodies, each of which were tested in less than five patients, although some other parameters were not analyzed for this paper.

Autoantibody levels were normal for most antigens, but 7 of 21 showed increased levels compared to laboratory normals for both rheumatoid factor and total immune complex. Patients tested through ISL typically had normal numbers of total helper and suppresser cells (CD4, CD8) and normal CD26 (TA1) cells. Results from the two laboratories may have differed because of different normal ranges, different patients being tested, and/or techniques; this merits further study. However, abnormalities in ISL tests did include higher than expected levels of chemical antibodies (11 of 24 patients), typically involving benzene, which is most likely encountered as a metabolite of aromatic petrochemicals. Reduced T-cell function was common (9 of 21 patients tested), with 7 of the 9 being abnormal using both concanavalin A (conA) and phylohemagglutinin (PHA), an indication of intratest consistancy. Impairment of B-cell function was seen in five patients, of whom four were abnormal in all three tests (pokeweed mitogen, lipopolysaccharide, *Staphalococcus aureus*). This consistency across tests increases the likelihood of their validity. While the measure of total NK cells was typically normal, function was impaired in 14 of 22 tested patients.

Immune indicators are likely to change significantly over time following exposure, with initial activation leading to a cascade of other immune changes and later resolution of activation. Thus, single immune measurements in a population with varying time intervals following various causal and significant aggravating exposures are likely to obscure certain abnormalities. The optimal way to study immune changes is to observe patients shortly after casual exposure and to follow them through time. The time interval to maximum immune activation and other immune responses and to return to preexposure levels, if ever, at this time is not known for chemically sensitive patients. Further, different immune measures are likely to peak at different time intervals following onset of illness.

For a patient whose chemical sensitivity was thought to be caused by occupational exposure to carbonless copy paper, we compared immune measurements before the patient left and after she returned to her job, which required sitting near and working with large quantities of carbonless copy paper (Table 6). These data suggest that immune measures pre- and postchallenge testing are unlikely to show major changes. The patient had been away from exposure for many months and showed significant clinical improvement. Chemical sensitivity has been seen in a hundred patients with substantial occupational exposure to carbonless copy paper (E Panitz, personal communication).

In 1994, a few physicians began testing for porphyrin disturbances in chemically injured patients previously diagnosed with MCS. Like patients with some types of congenital porphyria, chemically sensitive patients frequently describe intolerance to small amounts of alcohol and many synthetic (petrochemical) medications, ingestion of which provokes acute outbreaks of neurological and psychological symptoms such as imbalance, tremor, abdominal pain, and mood swings as well as symptoms or signs of autonomic involvement such as rapid heart rate and increased blood pressure. Patients also sometimes exhibit cutaneous symptoms of photosensitivity such as skin rashes and other lesions.

Intrigued by informal reports of porphyrin abnormalities being found in over 70% of MCS patients being tested (*57*), Ziem and her research associate, Albert

Donnay, developed a protocol for diagnosing disorders of porphyrin metabolism in chemically sensitive patients to try to control for the many variables that may affect testing for porphyrins and related enzymes (*58*). The protocol was developed in consultation with the porphyria laboratory of the Mayo Medical Laboratories and is based on Mayo's 1995 test catalog and its 1994 interpretive handbook. The protocol includes a one-page patient testing questionnaire (Appendix 3), most of which has been incorporated into the Health and Environmental History Questionnaire. It was surprising to learn from this questionnaire and verbal interviewing that even dark brown or red urine (not attributable to blood) was relatively common in MCS patients during more severe episodes of illness.

It appears that most of the patients questioned experienced significant porphyrialike neurological reactions (including sharp abdominal pain) when exposed to such well-known porphyrogenic stressors as alcoholic beverages (even a single drink was enough to trigger symptoms), usual therapeutic doses of many synthetic pharmaceuticals, and fasting or skipping meals. Most of those with skin symptoms also reported adverse reactions to sunlight exposure.

It was found that because of problems with memory, concentration, and general fatigue, patients often experienced difficulty understanding and following the necessary instructions. A separate patient testing questionnaire provided a double check on such compliance (Appendix 3). Since many biomarkers of neurological and neurocutaneous porphryinopathy commonly are known to be abnormal only during periods of acute attack, patients usually were advised to wait for testing until their symptoms were "worse than usual." Unfortunately, many went for testing without waiting for an exacerbation of their illness. Of the two biomarkers in urine associated with acute attacks of neurological congenital porphyrias, porphobilinogen was normal in 10 of 11 patients tested, and δ-aminolevulinic acid was normal in 7 of 8 tested. Despite lacking these indicators of acute attack, surprisingly 12 of the 14 nevertheless tested positive for a variety of other porphyrin-related abnormalities (defined here as any result outside Mayo's range of normal).

Of the 13 patients tested for 5 different urinary porphyrins, 8 had at least one abnormality. Four patients had only elevated coproporphyrins, 1 had only elevated pentacarboxylporphyrins, 2 had elevations in both of these, and 1 had elevated coproporphyrins and uroporphryins. Of the 11 patients with stool evaluations, 3 showed abnormalities: 1 had only elevated coproporhyrins, 1 had only elevated protoporphrins, and the third patient had elevated copro-, uro- and protoporphyrins. Those with elevated fecal coproporphyrins also had elevated urinary coproporhyrins. One patient submitted a stool specimen that Mayo felt was too small to represent a 24-hr sample, so this result was not included.

All patients were given blood tests for the activity of porphyrin-related enzymes. The most common enzyme deficiency was in the activity of coproporhyrinogen oxidase (CpgO), which was below normal in 9 of the 14 patients tested. CpgO was evaluated in reticulocytes in conjunction with a reticulocyte count which, because of lab confusion was done in most but not all patients. When completed, the reticulocyte counts were normal. The activity of both ALA-D and porphobilinogen deaminase (PbgD) was below normal in 7 of the 14 patients. Uroporphyrinogen decarboxylase and uroporphyrinogen III co-synthase activity was tested in 12 and 14 patients, respectively, and found to be normal in all cases. Only two patients had no enzyme deficiencies; four had one deficiency each, four had two each, and four had three each (ALA-D, PbgD, and CpgO). The enzymes affected here occur in cytosol and mitochondria (*59*), and the presence of disturbed enzymes in both these compartments suggests chemical injury to both mitochondrial and cytosol cellular areas.

Despite lack of a control group, it is difficult not to conclude that porphyrin disturbances are present in a substantial percentage of chemically sensitive patients. The multiple enzyme deficiencies found in many of these MCS patients (6 of 14) are not characteristically associated with any of the known types of congenital porphyria, which usually are marked only by a single enzyme deficiency or with secondary coproporphyrinuria due to other unrelated conditions, usually an isolated abnormality, unaccompanied by enzyme deficiencies. (Because of testing techniques at Mayo, when porphobilinogen deaminase is reduced, ALA-D can also appear to be reduced, so the presence of these two abnormalities together cannot be presumed to involve two enzymes.) Given also that none of the patients tested had known family histories of active or latent porphyria, the fact that such relatively rare abnormalities and porphyrialike symptoms were found in 12 of 14 patients strongly suggests that those with MCS suffer from an environmentally acquired rather than an inherited disorder of porphyrin metabolism. (A genetic predisposition cannot be ruled out conclusively without further testing the patients and family members, but statistically such a finding is highly unlikely, since congenital porphyrias are so rare.)

Although the porphyrin disturbances and enzyme deficiencies found in these MCS patients appear to be milder than in the acute types of congenital porphyria that primarily affect heme synthesis in the liver, other organs clearly are affected in cases of toxic exposure and chemical injury (e.g., irritant effects on the respiratory system, petrochemical neurotoxicity, immune dysfunction). These factors together with the involvement of multiple enzyme deficiencies may account for the somewhat more diverse symptomatology seen in MCS patients compared to those with strictly congenital porphyria. This certainly is the case with other toxically acquired porphyrinopathies such as the well-recognized forms caused by overexposure to lead, dioxin, and hexachlorobenzene, all of which, as neurotoxins, affect more than just heme synthesis and cause chemical injury unrelated to porphyrin abnormalities. Given all the above, it is not unreasonable to suspect that the different patterns of porphyrinopathy evident in MCS patients may be caused and/or exacerbated by these patients' own unique overexposures to specific toxic chemicals.

On the WAIS-R neuropsychological evaluation done by McTamney (Table 2), 6 of the 13 MCS patients tested showed a significant difference of 15 points between the verbal and performance phases of the test, all scoring higher on the verbal portion. Only one patient scored in the superior range for IQ with no apparent difficulties.

The Halstead-Reitan battery showed a number of significant scores indicating impairment (Table 3). On the Category test, 53% of patients scored in the impaired range. On the Tactile Performance test, 60% scored in the impaired range on the total time required to complete the three trials. None of the patients had problems with the dominant hand, while 30% were slower with the nondominant hand despite the previous trial with the dominant hand. Twenty-three percent of patients scored in the impaired range on the memory phase of the Tactile Performance test, while 84% scored in this range on the Localization Scale.

Table 4. Immune panels of 68 multiple chemical sensitivity patients tested by Antibody Assay Laboratory through March 1994.[a]

				Exposure substance	CD4		CD8		CD26		CD19		CD57		Autoantibodies					
					%	Total	%	Total	%	Total	%	Total	%	Total	SM	PC	BB	MI	NU	MY
ID	Sex	Loc.	Exposure situation	Lab normals	35–55%	480–1185	20–36%	220–865	0–8%	0–256	5–15%	60–400	15–22%	150–650	<1:20	<1:20	<1:20	<1:20	<1:20	<1:8
1	F	OCP	Vent cleaning	Mineral spirits, toluene propane	34*	748	30	660	10*	220			10*	220	N	N	P*	N	N	P*
2	F	SCH	Pesticide residue	Chlordane chlorpyrifos		836		462		308*					P*	N	N	N	N	P*
3	M	SCH	Pesticide residue	Chlordane chlorpyrifos		912		696		288*					N	N	N	N	P*	N
4	F	SCH	Pesticide residue	Chlordane chlorpyrifos		1260*		630		900*					N	N	N	N	N	N
5	M	OCP	New computers	Computer offgassing	48	1296*	20	540	18*	486*	13	351			P*	N	N	N	N	N
6	M	SCH	Pesticide residue	Chlordane chlorpyrifos		828		391		230					P*	N	N	N	N	P*
7	M	SCH	Pesticide residue	Chlordane chlorpyrifos		1400*		805		595*					N	N	N	N	N	P*
8	F	OCP	Carbonless paper	Formaldehyde	54	1404*	19*	494	28*	728*	3*	78			N	N	N	N	N	N
9	F	SCH	Pesticide residue	Chlordane chlorpyrifos		1035		575		483*					N	P*	N	N	N	P*
10	M	OTH	Pesticide residue	Chlorpyrifos	52	1300*	23	575	17*	425*	4*	100			N	N	N	N	N	P*
11	F	OCP	New carpet, adhesive	4-Phenylcyclohexene, etc.	49	1323*	28	756	31*	837*	7	189			N	N	N	N	N	P*
12	F	OCG	Postal employee	Epoxy paint	35	1575*	24	1080*	14*	630*	2*	90	5*	225	N	N	N	N	N	P*
13	F	SCH	Pesticides, painting	Malathion, solvents	46	1150	20	500	8	200	6	150	4*	100*	N	N	N	N	N	N
14	F	OCG	Roof repair	Isocyanates	36	828	22	506	19*	437*	4*	92			P*	N	N	N	N	N
15	F	OTH	Anesthesia, head injury	Anesthetic agent unknown	42	1134	27	729	19*	513*	5	135			N	N	N	P*	N	N
16	M	OTH	Pesticide residue	Not known	35	910	19*	494	19*	494*	3*	78			P*	N	P*	N	N	N
17	M	OTH	Pesticide residue	Chlorpyrifos		960				540*					N	N	N	N	N	P*
18	M	HOM	Fiberglass insulation	Phenolformaldehyde	32*	864	16*	432	14*	378*	11	297			N	N	N	N	P*	N
19	F	HOM	Fiberglass insulation	Phenolformaldehyde	39	780	17*	340	9*	180	8	160			N	N	N	N	N	N
20	M	HOM	Fiberglass insulation	Phenolformaldehyde	36	720	13*	260	13*	260*	2*	40*			P*	N	N	N	N	N
21	F	HOM	Fiberglass insulation	Phenolformaldehyde	24*	480	8*	160*	13*	260*	1*	20*			P*	N	N	N	N	N
22	F	OCP	Pesticide residue	Chlorpyrifos	40	880	16*	352	10*	220	8	176			N	N	N	N	N	N
23	M	OCP	Maintenance worker	Toluene methylene chlorine	45	603	21	282	22*	295*	10	134			P*	N	N	N	N	N
24	M	OCP	Incinerator smoke	Combustion products	34*	782	14*	322	15*	345*	3*	69			P*	N	N	N	N	P*
25	F	OCG	Roof tar, new paint	Offgassing combination	38	608	16*	256	11*	176	7	112			P*	N	N	N	N	P*
26	F	OCG	Vent cleaning	Butoxyethanol and others	42	714	11*	187*	18*	306*	1*	17*			P*	N	N	N	N	P*
27	F	HOM	Roofing compound	Isocyanate (MDI)	33*	561	38*	646	25*	425*	9	153	6*	102*	P*	N	P*	N	N	P*
28	F	OTH	Battery fumes, overheating	Combustion products	39	1092	21	588	15*	420*	2*	56*			P*	N	P*	N	N	P*
29	F	HOM	Pesticide residue	Malathion, other pesticide	58*	1450*	20	500	20*	500*	3*	75			P*	N	N	N	N	N
30	M	HOM	Pesticide residue	Chlorpyrifos	54	1134	22	462	19*	399*	3*	63			N	N	N	N	N	N
31	M	OCP	New Carpet adhesive	4-Phenylcyclohexene, etc.	29*	899	22	682	12*	372*	1*	31*			N	N	N	N	N	P*
32	M	OCG	Renovation floor tile	Glycol ethers and other	60*	1320*	33	726	3	66			14	308	P*	N	P*	N	N	N
33	F	STU	Pesticide residue	Chlordane		1485*		702		486*					P*	N	N	N	N	N
34	F	OCP	New carpet	Offgassing combination	37	999	24	648	21*	567*	4*	108			N	N	N	N	N	N
35	F	OCP	Leaking underground	Gasoline	46	1840*	36	1440*	13*	520*	2*	80			N	N	N	N	N	P*
36	F	HOM	Pesticide exposure	Chlordane chlorpyrifos	44	1760*	20	800	14*	560*	12	480*			P*	N	P*	N	N	N
37	F	OCP	Hospital linen	Fabric softener	38	1178	18*	558	6	186	3*	93			N	N	N	N	N	P*
38	F	HOM	Exposure to cloth[b]	Petrochemicals	54	702	23	299	24*	312*	8	104			P*	N	N	N	N	N
39	F	OCP	Research lab chemicals	Petrochemicals	45	855	32	808	21*	399*	9	171			N	N	N	N	P*	N

Table 4. (*Continued*).

ID	Sex	Loc.	Exposure situation	Exposure substance / Lab normals	CD4 % 35–55%	CD4 Total 480–1185	CD8 % 20–36%	CD8 Total 220–865	CD26 % 0–8%	CD26 Total 0–256	CD19 % 5–15%	CD19 Total 60–400	CD57 % 15–22%	CD57 Total 150–650	Autoantibodies SM <1:20	PC <1:20	BB <1:20	MI <1:20	NU <1:20	MY <1:8
40	F	OCP	Dental assistant	Glutaraldehyde	45	1170	22	572	9*	234	3*	78	18	468	N	N	N	N	P*	N
41	F	OCP	Circuit board dust	Methylene chloride	29*	522	25	450	14*	252	5	90			N	N	N	N	N	N
42	F	HOM	Reclamation	Aliphatic petro distillation	43	903	12*	252	9*	189	2*	42*			N	N	N	N	N	N
43	M	HOM	Reclamation	Nonylphenoxy polyethylene	38	836	19*	418	15*	330*	3*	66			P*	N	N	N	N	P*
44	F	OCP	Office worker	TDI, tertiary amine catalyst	50	1050	28	588	20*	420*	6	126			N	N	N	N	N	N
45	F	OCP	Office worker	Chlordane	36	756	20	420	21*	441*	1*	21*			P*	N	N	N	N	P*
46	M	HOM	Exposure to cloth[b]	Petrochemicals	48	1344*	25	700	19*	532*	2*	56*	1*	28*	P*	N	P*	N	N	N
47	F	OCP	Solvent in assembly line	MIK, MEK, F, and MS	32*	672	21	441	19*	399*	1*	21*			P*	P*	N	N	P*	P*
48	F	HOM	Herbicide	Pendamethalin	34*	816	23	552	9*	216	2*	48*	5*	120*	N	N	N	N	N	P*
49	F	OCG	Building-related exposure	Diazinon	52	1716*	21	693	37*	1221*	2*	66			P*	N	N	N	N	N
50	F	OCG	Insulation, fiberglass	Phenol formaldehyde	46	874	22	418	27*	513*	6	114			P*	N	N	N	N	P*
51	M	OCP	UV ink	Ketone trimethylol propalene	38	912	17*	408	23*	552*	2*	48*			P*	N	N	N	N	P*
52	F	OCG	New building	Dichlorobenzene butoxy.	45	675	20	300	15*	225	2*	30*			P*	N	N	N	N	P*
53	F	HOM	Reclamation	Nonylphenoxy polyethylene	31*	496	13*	208*	14*	224	3*	48*			P*	N	N	N	N	N
54	F	OCG	New carpet, adhesive	4-Phenylcyclohexene, etc.	44	924	22	462	15*	315*	11	231			N	N	N	N	N	N
55		OCG	Tight building, new carpet	Offgassing combination	42	588	24	336	18*	252	2*	28*			P*	N	P*	N	N	P*
56	M	OCG	Workplace exposure	Chlorpyrifos, Cypermethrine	26*	650	16*	400	20*	500*	5	125			P*	N	N	N	N	N
57	F	OCG	Renovated building	Methanol dibutyl phthalate	34*	612	24	432	15*	270*	2*	36*			P*	N	P*	N	N	P*
58	M	OCP	Inks, carbonless paper	Multiple solvents	38	836	22	484	15*	330*	3*	66			N	N	N	N	N	N
59	M	OCP	Tile setter	Hexane, toluene, acetone	45	1260*	34	952*	17*	476*	1*	28*			P*	N	N	N	N	N
60	F	HOM	Malfunctioning H_2O heater	Natural gas	58*	1508*	21	546	24*	624*	2*	52*			P*	N	N	N	N	N
61	F	HOM	Pesticide	Chlordane	44	1408*	29	928*	18*	578*	12	384	8*	256	P*	N	N	N	N	N
62	M	HOM	Pesticide	Chlordane	46	966	14*	294	25*	525*	9	189	1*	21*	N	N	N	N	N	N
63	M	OCG	New carpet, tight building	Offgassing combination	38	760	25	500	9*	180*	5	100			P*	N	N	N	N	P*
64	F	OCP	New carpet, adhesive	Offgassing combination	53	1696*	15*	480	22*	704*	9	288	13*	416	N	N	N	N	N	P*
65	F	HOM	Not known	Not known	50	1150	31	713	10*	230	12	276	8*	184	N	N	N	N	N	N
66	F	OCP	Original exposure unknown	Styrene solvents	39	1209*	20	620	9*	279*	4*	124	9*	279	P*	N	P*	N	P*	N
67	F	OCP	Lab employee, spill	Methylisoamyl ketone	48	1296*	36	972*	19*	513*	2*	54*	20	540	N	N	N	N	N	P*
68	F	OCG	Carpet shampoo	Sodium lauryl sulfate	72*	1944*	16*	432	27*	729*			12	324	P*	N	P*	N	N	P*
Average result					1016		534		415*		1147*									
% Abnormal					27%	31%	33%	12%	95%	76%	62%	34%	73%	33%	53%	3%	15%	2%	9%	43%

Abbreviations: MIK, methyl isobutyl ketone; MEK, methyl ethyl ketone, F, formaldehyde; MS, mineral spirits. Key: * Indicates abnormal result; Blank entry, not tested. Location code (Loc.): OCP, occupational exposure, private sector; OCG, occupational exposure, government/public sector; HOM, home; SCH, school; OTH, other. Autoantibody code: SM, smooth muscle; PC, parietal cell; BB, brush border; MI, mitochondrial; NU, nuclear; MY, myelin. [a]Not the same patients as in Table 5. [b]Laboratory chemical.

Table 5. Immune panels of 23 multiple chemical sensitivity patients tested by Immunosciences Laboratory from April 1994.

ID	Sex	CD4 Total	CD8 Total	CD26 Total	Chemical antibodies	T-cell function				
						GGT	SIgA	D-GA	conA	PHA
Normals ——→		336–2376	192–1598	0–432	IgE, IgG ≤ (16) IgM ≤ (64)	5–35 U/ml	10–28 µg/ml	1–5 mol/mol crea	75–100%	75–100%
1	M	1270	610	270	IgG BEN (32)*	NT	NT	NT	85	78
2	F	1740	250	320	IgG BEN (24)*	232*	NT	NT	50*	52*
3	F	1100	450	220	IgG ISO (24)*, IgG BEN (72)*	10	NT	NT	58*	61*
4	M	760	660	180	IgG BEN (24)*	23	4*	5	NT	NT
5	F	1400	680	410	IgG TMA (24)*, IgG BEN (40)*	21	NT	NT	62*	75
6	F	1200	660	160	IgG BEN (32)*	10	17	3	68*	65*
7	F	640	370	130	IgM TMA (200)*	12	9*	5	75	78
8	M	660	510	820*	All normal	34	4*	5	61*	62*
9	F	1572	489	102	All normal	20	9*	5	88	82
10	M	802	511	150	All normal	18	4*	7*	80	75
11	M	1313	586	224	All normal	27	13	5	75	78
12	F	1080	301	31	All normal	13	NT	5	66*	72
13	F	1120	1030	250	IgG FOR (64)*, IgG ISO (64)*, IgG TMA (32)*, IgG PA (32)*, IgG BEN (64)*	16	1*	4	88	82
14	F	1080	650	110	All normal	18	NT	4	80	75
15	F	1120	900	120	All normal	22	8*	4	76	79
16	M	590	620	80	All normal	20	15	6*	NT	NT
17	F	1090	480	150	IgM BEN (96)*	18	NT	NT	59*	62*
18	F	790	360	130	All normal	11	NT	NT	63*	65*
19	M	870	570	180	All normal	9	25	4	79	76
20	F	1400	800	370	All normal	6	25	4	82	84
21	F	1180	300	170	IgM BEN (128)*	15	4*	5	79	78
22	F	580	190	70	IgG BEN (24)*	10	NT	NT	89	110*
23	F	860	770	170	All normal	27	4*	4	61*	92
		1053	554	209	←—— Average					
		0	0	4%	←—— % Abnormal ——→	5%	64%	13%	43%	30%

Abbreviations: conA, concanavalin A; crea, creatinine; D-GA, D-glucaric acid (urine); GGT, gamma-glutamyltransferase; icNK, immunocompetent NK; LIP, lipopolysaccharide; LUs, lytic units; NT, not tested; PHA, phytohemagglutinin A; PWM, pokeweed mitogen; SIgA, secretory IgA; StA, *Staphaloccoccus aureus*. Autoantibody codes: MC, myocardial; MI, mitochondrial; MS, microsomal; PC, parietal cell; RF, rheumatoid factor; SM, smooth muscle; ST, striated muscle; TG, thyroglobulin; TIC, total immune complex. Chemical antibody codes: BEN, benzene; FOR, formaldehyde; ISO, isocyanates; PA, phthalic anhydride; TMA, trimellitic anhydride. *, abnormal results.

Table 6. Immune panels of a multiple chemical sensitivity patient before and after exposure to carbonless copy paper.

Immune tests performed by Immunosciences Laboratory (ISL)	ISL normal ranges	Before patient's exposure, 10/10/94	After patient's exposure, 10/13/94
Lymphocytes	960–4320	1568	2088
T-cells	701–3788	1150	1550
T helpers	336–2376	790	1090
T suppressers	192–1598	360	480
B-cells	48–648	300	420
Natural killer cells	52–864	110	167
Immunocompetent NK cells	14–216	16	21
TA1	0–432	130	150
Gamma-glutamyltransferase	4–22	11	18
IgG myelin basic protein	0–100	25	40
IgM myelin basic protein	0–50	10	20
IgA myelin basic protein	0–20	15	10
Total immune complex	0–50	14	7
IgM trimellitic anhydride*	0–64	8	32
IgM benzene*	0–64	8	64
PHA	75–100	65	62
conA	75–100	63	59
NK activity	20–50	15.29	5.26

*, other chemical antibodies were tested but only those shown increased.

The Rhythm Test showed 53% in the impaired range, whereas the Speech Sounds Perception Test showed 46% in the impaired range. On the Finger Oscillation Test, 53% scored in the impaired range with the dominant hand and 61% for the nondominant hand. Trails A had 53% in the impaired range, whereas Trails B showed 61%. The overall Impairment Index scores showed 53% impairment. The most common neurologic changes on the physical exam were reduced vibratory perception (hands) and abnormal Romberg (suggesting vestibular neuropathy).

Discussion

Chemically sensitive patients from a medical practice, who often have experienced different initiating exposures, may have different patterns of porphyrin disturbance, as was found in this study. This is the pattern to be expected from the literature on acquired porphyrin disturbance. Future research on porphyrin abnormalities should compare results by type of original exposure and by type and level of current

B-cell function			Natural killer cell			Autoantibodies								
PWM	LIP	StA	Total	Subtotal icNK	Function	TG	MS	ST	PC	MI	SM	MC	RF	TIC
75–100%	75–100%	75–100%	52–864 mm^3	14–216 mm^3	20–50 LUs	<1:20	<1:20	<1:20	<1:20	<1:20	<1:20	<1:20	<20 IU/ml	0–50 µg eq/ml
76	78	81	365	73	12.54*	1:10	1:40*	1:40*	1:20	1:10	1:10	1:10	8	56*
69*	65*	68*	248	25	19.45*	1:10	1:10	1:20	1:20	1:10	1:20	1:15	8	89*
65*	67*	69*	245	20	44.83	1:10	1:10	1:10	1:20	1:10	1:20	1:10	13	23
NT	NT	NT	246	41	NT	1:20	1:10	1:20	1:50*	1:10	1:20	1:10	25*	9
76	79	76	108	27	3.58*	1:10	1:10	1:15	1:20	1:10	1:15	1:10	29*	25
72*	69*	66*	318	23	21.84	1:10	1:10	1:15	1:20	1:10	1:20	1:10	16	38
81	76	79	105	12*	7.6*	1:10	1:10	1:20	1:30*	1:10	1:30*	1:15	28*	38
58*	64*	63*	220	16	14.62*	1:10	1:10	1:15	1:10	1:10	1:10	1:10	22*	32
86	84	83	204	13*	46.21	1:20	1:20	1:20	1:20	1:10	1:20	1:20	8	36
83	84	85	61	42	13.45*	1:20	1:20	1:20	1:20	1:10	1:10	1:10	3	25
77	79	81	202	21	65*	1:20	1:20	1:20	1:20	1:10	1:10	1:10	8	35
74	75	77	43*	10*	11*	1:20	1:20	1:20	1:20	1:20	1:20	1:40*	2	56*
92	96	91	281	125	37.1	1:10	1:10	1:30*	1:30*	1:10	1:20	1:20	12	52*
85	85	85	194	22	>100*	1:35*	1:10	1:10	1:10	1:10	1:10	1:20	31*	69*
81	84	80	243	24	3.26*	1:10	1:10	1:10	1:10	1:10	1:10	1:20	3	15
NT	NT	NT	239	15	12.96*	1:10	1:10	1:10	1:15	1:10	1:15	1:15	1	82*
76	75	80	167	21	5.26*	1:10	1:25*	1:10	1:10	1:10	1:10	1:10	1	7
79	84	76	110	16	15.29*	1:10	1:10	1:10	1:10	1:10	1:10	1:10	1	14
75	76	75	237	59	13.68*	1:10	1:10	1:10	1:20	1:10	1:20	1:20	33*	33
78	83	85	399	29	>100*	1:10	1:10	1:10	1:10	1:10	1:10	1:10	1	31
81	84	82	379	21	7.36*	1:20	1:20	1:20	1:20	1:10	1:20	1:20	17	30
77	81	76	134	11*	14.15*	1:10	1:10	1:10	1:20	1:10	1:20	1:10	16	43
75	78	76	300	21	56.95	1:10	1:10	1:10	1:25*	1:10	1:25*	1:15	22*	79*
17%	19%	19%	4%	17%	77%	4%	9%	9%	17%	0	9%	4%	30%	30%

symptoms, with patients tested consistently during both acute and nonacute phases.

Discrepancies are found between our immune testing results and those of Simon et al. (*60*). Simon found significantly lower TA1/CD26 cell activation among MCS patients compared to that of a group of controls from a musculoskeletal clinic, whereas our results from AAL and the literature show higher values compared to those of normal reference ranges following chemical exposure. It is possible a coding error occurred in the Simon study; raw data should be made available to independent researchers. Ziem personally coded immune data for Table 4, but it could also be independently reviewed. Since both studies used AAL, this extent of discrepancy is unexpected.

Other confounding problems exist with the Simon data, which is often cited because it uses a control group. However, the control group is problematic in the Simon study because it consists of patients seen in a musculoskeletal clinic who were not screened for MCS, chronic fatigue syndrome, or fibromyalgia. The latter are both more common diagnoses whose symptoms have been found to overlap those of multiple chemical sensitivity (and of each other) so as to be almost indistinguishable in as many as 67% of all cases (*45,61*). Musculoskeletal controls certainly would be expected to include patients with inflammation of joints, muscles, and/or connective tissue in whom cellular immune changes of inflammation also could be present. In addition, these controls are likely to be taking medication for pain, a frequent reason for clinic visits in such patients. Patients taking medication for pain are not an appropriate control group for neurocognitive test comparisons, which also were reported in this study. We believe the clinical records of Simon's control patients should be independently reviewed to evaluate for fibromyalgia, chronic fatigue, chemical sensitivity, inflammatory processes, and use of pain medication.

Both the control and study groups' raw data for the TA1/CD26 parameter also should be independently reviewed. Simon attributes his study's unusual immune findings to the laboratory's poor reliability, which he asserts is "no better than chance on most of their measures," but he also admits that these critical data on test reproducibility were not published in his paper (*56*). Given these problems, and the reports of immune abnormalities here and by other authors, it appears that the issue of cellular immune disturbance in chemically sensitive patients needs further study.

Immune response probably varies greatly with time and appears to differ with different types of exposures. Immune studies should evaluate exposed individuals over time, beginning as soon as feasible after causal exposures and following for several years. Major immune changes may not be seen following acceptable challenge doses; the patient whose immune measures increased mildly to moderately with return to workplace exposure (Table 6) had serious exacerbation of many clinical symptoms lasting several months. This level of exposure with accompanying symptoms would not be acceptable as a clinical chamber challenge.

Failure to follow chemically sensitive patients over time leads to lack of understanding of responses to exposures and of

removal from exposure. We are following more than 300 chemically sensitive patients and have observed both significant clinical improvement with reduced exposures and clinical exacerbation on reexposure (including increased abnormalities on exam and laboratory testing). This is a clinical impression, although it is not quantified in aggregate for this paper. It appears that to date the professionals who have published studies suggesting a psychological origin of chemical sensitivity do not follow these patients over time, do not remove them from exposure and observe responses and then return them to exposure and observe responses. Also, these researchers are not physicians treating patients for the disorder, and therefore are not able to observe the ongoing clinical course of the illness.

We reported onset of chemical sensitivity shortly following exposure to a wide variety of petrochemicals, combustion products, and irritants (Table 4). In some cases these were discrete events such as leaks, spills, or other acute exposure events. Often, especially in occupational settings, exposures were chronic. Typically, in these situations the illness began as a more limited sick-building syndrome, which with further exposure developed into chronic illness with associated chemical sensitivity. This suggests that exposure controls in the early phase may prevent the more disabling phase, and that sick-building syndrome is a more self-limited form of chemical sensitivity.

The combined abnormalities of the immune, respiratory, porphyrin, and nervous systems discussed here are incompatible with a psychologic etiology for chemical sensitivity. A systematic review of ten recent studies purporting to show a psychologic origin for chemical sensitivity revealed serious methodologic flaws in all studies including the Simon study, sufficient for the reviewing authors to conclude that none of the studies had the methodologic strength to determine that chemical sensitivity was psychologically induced (*40*).

Vasospasm appears to be a problem in chemically sensitive patients. Most of our patients noted frequent headaches that often were consistent with migraine and diagnosed as such by other evaluating physicians. Migraine is known to be triggered by chemical odors (*62*) and involves abnormal vasospasm. Cerebral vasospasm with reduced cerebral blood flow has been reported with encephalopathy following solvent exposure (*63*) and in patients with chemical sensitivity (*42,64,65*). One of our patients developed new onset of Raynaud's phenomenon (a vasospastic disorder), which we observed to be triggered by double-blinded finger contact with carbonless copy paper (the probable cause of her chemical sensitivity). Only a few patients developed new onset of high blood pressure (another vasospastic response), which is seen primarily following exposure (their blood pressure readings usually remained normal between exposures). These vasospastic responses may involve abnormal autonomic function, which has been observed to occur with chemical sensitivity (*35*).

Diagnoses of fibromyalgia and chronic fatigue syndrome are common among our MCS patients (currently 75 and 85%, respectively). We recommend further research on the incidence of chemical sensitivity in these groups using the types of screening questionnaires developed by Kipen, Bell, and Davidoff. If these disorders are essentially the same, much of the research already done for fibromyalgia and chronic fatigue syndrome may also apply to MCS; this could reduce research costs and time delays. Increased sensitivity to chemicals also occurs with migraine, asthma, and other disorders. However, fibromyalgia syndrome, chronic fatigue syndrome, and porphyrin disorders are multiple-system disorders involving chemical sensitivity.

Over one-third of our patients described tremor several times or more a month (Figure 1). Several patients were told by other physicians that they were developing Parkinson's disease during more serious periods of their illness only to have the diagnosis rescinded when they improved after environmental controls were put in place to reduce exposures. Parkinson's disease has been reported following pesticide exposure (*66*).

Nearly half our patients reported increased symptoms during or after swimming in a chlorinated pool (Figure 3), which has been associated with increased chloroform levels (*67*). Patients also often reported reduced symptoms during and after showering with, compared to without, an activated charcoal filter that helps remove chloroform. Longer showers and/or those with greater flow rates release more chloroform and other chlorinated products. Water filters that reduce chlorine therefore appear to be a reasonable control for MCS.

In addition to filters for chlorinated water, other reasonable means exist to control exposures that aggravate MCS symptoms. Aggravation from vehicle exhaust (Figure 2) can be reduced by using an auto filter device that provides activated charcoal filtration and by avoiding ozonating devices which generate irritants. Symptom exacerbation from pesticides, cleaning products, building materials, etc. can be reduced by using less toxic products. Reasonable accommodation at the work place, at home (apartments, condominiums, etc.) and at school and public areas could be available to those with this debilitating condition by requesting that less toxic products and procedures be used. Further helpful suggestions are discussed in our Environmental Control Plan (*68*).

In our 10-year experience with chemically sensitive patients, no patients lost their sensitivity to chemicals. No patients were able to go to problem environments (new carpets, recent pesticides, etc.) consistently without deterioration of their conditions. Thus, MCS should be considered a permanent condition. Some patients were able to continue working if their employers provided nontoxic accommodations for their conditions. More than half the patients continued to be too sick to work under the prevailing conditions at the work place. We believe this proportion could be reduced if society pays more attention to use of nontoxic products.

The large and growing epidemic of chemical sensitivity in the United States is partly because of inadequate exposure limits for chemicals. These exposure limits have been shown to lack scientific merit (*69*) and to have been seriously influenced by vested interests (*70–73*). Exposures that cause MCS at home or the work place sometimes reflect relatively widespread practices or products, some of which may be within legal limits. Many aggravating exposures are probably below legal limits but often do not provide an adequate safety margins even for the healthy population (*69*). The widespread indoor use of pesticides in U.S. schools, homes, work places, and public buildings is in striking contrast to practices in Germany and Scandinavia. Major policy changes with regard to chemical product formulation and use will be necessary to reduce future cases of permanent chemical sensitivity as well as to reduce disability for currently affected patients.

Summary

Most of our patients with symptoms of MCS appear to have developed chronic illness following exposure to petrochemicals, combustion products, and other irritants. Symptoms and signs in patients

reporting chemical sensitivity suggest involvement of the immune, respiratory, limbic, and other nervous systems (central, peripheral, autonomic) as well as impaired porphyrin metabolism. This suggests that multiple mechanisms of chemical injury probably are involved, all of which can intensify response to an exposure. Immune activation, neurogenic inflammation (*74*), kindling (*75*), and/or time-dependent sensitization (*76*) can amplify the body's response to chemical exposure in the immune system, respiratory system, and nervous system. It is possible that impaired porphyrin metabolism reduces the amount of heme available for cytochrome P450, part of the liver's major detoxification system for foreign chemicals, which could result in intensified symptoms for a wide range of exposures.

Research strategies are needed that allow evaluation of multiple sites of chemical injury and multiple mechanisms of injury—almost all studies to date focus on only one type of chemical injury.

Immune activation also could lead to increased response to foreign substances, such as conventional allergens. We note in our patients an apparent high rate of new onset of allergies to mold, dander, etc., following onset of chemical sensitivity. Kipen reports what appears to be a significant level of sensitivity to chemicals among asthmatics (*77*). Asthma also is increased with higher levels of indoor volatile organic compounds (VOCs), formaldehyde and/or limonene (*78*). Persons with other allergic diatheses also should be studied for sensitivity to chemicals. If indeed chemical exposure via immune activation contributes significantly to the high and increasing rates of allergies, we may have the means to counter this alarming trend.

Studies of chemically injured populations should compare MCS patients with specific and identifiable initial exposures to MCS patients who cannot identify any specific triggering exposure. Other patient groups that should be studied for MCS include those with recurring migraines, chronic sinusitis or rhinitis, degenerative neurologic diseases (such as acute types of congenital porphyria), autoimmune disorders (such as multiple sclerosis, autoimmune hepatitis, rheumatoid arthritis, and lupus), hyperactive children, and patients with attention deficit disorder. Chemically exposed groups also merit study, especially those that have avoided further occupational exposures following work with pesticides, solvents, etc. We believe such studies will find levels of chemical sensitivity in these subpopulations that are considerably greater than currently recognized.

Appendix 1. Question 14 from Ziem's Health and Environmental History Questionnaire

14. For the symptoms and health problems listed below, if you have had the problem in the last year, **CIRCLE** the number that best describes how often the symptom occurs, or circle 7 if not sure.

Daily to Almost Daily	Several Times/ Week	Once A Week	Several Times/ Month	Once/ Month Or Less	Rarely If Ever	Not Sure
Headache						
1	2	3	4	5	6	7
Numbness, tingling						
1	2	3	4	5	6	7
Weakness in a body part						
1	2	3	4	5	6	7
Lightheadedness, dizziness						
1	2	3	4	5	6	7
Tremor or shaking						
1	2	3	4	5	6	7
Muscle twitching						
1	2	3	4	5	6	7
Confusion, spaciness, inability to concentrate						
1	2	3	4	5	6	7
Memory problems						
1	2	3	4	5	6	7
Slurred words, difficulty finding words						
1	2	3	4	5	6	7
Coordination difficulties						
1	2	3	4	5	6	7
Low energy, fatigue (unusual)						
1	2	3	4	5	6	7
Dizziness when standing up after sitting						
1	2	3	4	5	6	7
Shakiness relieved with eating						
1	2	3	4	5	6	7
Poor appetite						
1	2	3	4	5	6	7
Sweet Cravings						
1	2	3	4	5	6	7
Unusual thirst						
1	2	3	4	5	6	7
Itchy, watery eyes or nose						
1	2	3	4	5	6	7
Visual changes						
1	2	3	4	5	6	7
Ringing ears						
1	2	3	4	5	6	7
Changes in hearing						
1	2	3	4	5	6	7
Nasal symptoms (discharge, stuffiness)						
1	2	3	4	5	6	7
Sinus discomfort						
1	2	3	4	5	6	7
Throat discomfort (soreness, tightness)						
1	2	3	4	5	6	7
Weak voice, hoarseness						
1	2	3	4	5	6	7
Fever						
1	2	3	4	5	6	7
Reduced cold tolerance						
1	2	3	4	5	6	7
Reduced heat tolerance						
1	2	3	4	5	6	7
Swollen glands						
1	2	3	4	5	6	7
Coughing						
1	2	3	4	5	6	7
Chest discomfort (heaviness, pain)						
1	2	3	4	5	6	7

Daily to Almost Daily	Several Times/ Week	Once A Week	Several Times/ Month	Once/ Month Or Less	Rarely If Ever	Not Sure
Chest tightness						
1	2	3	4	5	6	7
Wheezing						
1	2	3	4	5	6	7
Muscle discomfort, spasm						
1	2	3	4	5	6	7
Joint discomfort						
1	2	3	4	5	6	7
Rapid pulse						
1	2	3	4	5	6	7
Palpitations (rapid, violent throbbing, extra, or skipped heartbeats)						
1	2	3	4	5	6	7
Swelling of ankles						
1	2	3	4	5	6	7
Swelling (throughout body)						
1	2	3	4	5	6	7
Bruising without a cause						
1	2	3	4	5	6	7
Itching, rash, hives						
1	2	3	4	5	6	7
Flushing skin						
1	2	3	4	5	6	7
Reduced bladder control						
1	2	3	4	5	6	7
Need to pass urine frequently						
1	2	3	4	5	6	7
Insomnia						
1	2	3	4	5	6	7
Frequent jerking in sleep						
1	2	3	4	5	6	7
Other sleep disturbance						
1	2	3	4	5	6	7
Fingertips turning white or blue						
1	2	3	4	5	6	7
Menstrual Changes (women)						
1	2	3	4	5	6	7
Impotence, reduced ability for erection (men)						
1	2	3	4	5	6	7
Significantly reduced sex drive						
1	2	3	4	5	6	7
Other sexual problems						
1	2	3	4	5	6	7
Difficulty or discomfort with swallowing						
1	2	3	4	5	6	7
Reflux of stomach acid						
1	2	3	4	5	6	7
Nausea, vomiting, bloating, gas						
1	2	3	4	5	6	7
Abdominal discomfort (pressure, pain, cramps)						
1	2	3	4	5	6	7
Brown , green, or red urine-not due to blood						
1	2	3	4	5	6	7
Symptoms increased in sunlight						
1	2	3	4	5	6	7
Rash when exposed to sunlight						
1	2	3	4	5	6	7
Other (specify):						
1	2	3	4	5	6	7

Appendix 2. Question 6 from Ziem's Health and Environmental History Questionnaire

6. For each situation described below, answer the questions at the top of each column. By "sick," we mean anything that YOU consider to be either a major or a minor health problem.

Exposures:	**a.** Would you be sick if you had to spend 4 hours...?					**b.** Would you be sick if you had to spend 20 minutes ...?				
	No	A Little	Moderately	A Lot	Don't Know	No	A Little	Moderately	A Lot	Don't Know
a. Next to someone smoking cigarettes outside.										
b. Driving in heavy traffic with windows open.										
c. Around workers tarring a road.										
For the next questions, assume you are inside with no open windows...										
d. In a room sprayed with pesticides 4 hours ago.										
e. In a room painted 24 hours ago with water-based paint.										
f. Shopping in an enclosed mall.										
g. In a room with wall-to-wall carpet (1 week old).										
h. Sitting next to a person wearing perfume/cologne.										
i. Cooking on a stove using natural gas.										
j. Being around or using carbonless copy paper										
k. Sitting next to someone with fabric softener on clothing.										

Would you be sick if you had to ...?	No	A Little	Moderately	A Lot	Don't Know
l. Drink one glass of city (chlorinated) water.					
m. Try on newly dry cleaned clothing.					
n. Walk down the detergent aisle at a grocery store.					
o. Use self-serve at a gas station.					
p. Use a bathroom with a scented air freshener.					
q. Read a freshly printed newspaper.					
r. Wear synthetic fabrics.					
s. Swim for 20 minutes in a chlorinated pool.					
t. Wear clothing that has been laundered in chlorine bleach.					
u. Wear clothing laundered with perfumed laundry soap.					
v. Use chlorine bleach in your toilet.					

Appendix 3. Patient Testing Questionnaire from Protocol for Diagnosing Disorders of Porphyrin Metabolism in Chemically Sensitive Patients by Donnay and Ziem

PATIENT TESTING QUESTIONNAIRE

This questionnaire is needed for the evaluation of chemically-sensitive patients.
Please complete all questions after your testing and return this promptly to your doctor.

Patient Name:_____ ❑Gulf War Vet ❑Silicone Exposure ❑Pesticide Exp.

Address:_____ ❑Other Exposure:_____

City/Zip: _____ Age:_____ Sex: ❑Male ❑Female

Home Phone:(_____)_____-_____ Date Today: _____

Date Blood Drawn:_____ Time Blood Drawn (check): ❑ Morning ❑ Afternoon

Date Urine Collection Finished: _____ Date Stool Collection Finished: _____

Answer all the following but not until AFTER your tests are completed.	YES	NO	NOT SURE
1. For Any Tests, did you take any medications in the 2 weeks before testing?	____	____	____
IF YES, list the medications you took and the dates you took them: _____			
2. For Any Tests, did you drink any alcohol in the 2 weeks before testing?	____	____	____
IF YES, list the dates you drank, what you drank, and the approx. quantities: _____			
3. For Blood or Plasma Tests (in addition to above), did you eat any food or drink (besides water) in the 12 hours before testing?	____	____	____
IF YES, list what you ate or drank and when: _____			
4. Do you have skin symptoms made worse by exposure to sunlight?	____	____	____
5. Has your urine ever been ❑dark brown or ❑pink to red (not due to blood)? (Urine may darken with standing. Try to observe for this.)	____	____	____
IF YES, was this shortly after an exposure that increased your symptoms?	____	____	____
IF YES, when was the last time? Approximate Date:_____			
6. Do you have abdominal pain?	____	____	____
IF YES: Is this pain chronic ❑ ? Is this pain worse after an exposure ❑ ?			
7. Are any of your symptoms made worse by dieting or skipping meals?	____	____	____
8. Are any symptoms made worse by drinking just one glass of beer or wine?	____	____	____
9. Are any symptoms made worse by some medications?	____	____	____
10. Do you get any skin symptoms from medications or chemical exposures?	____	____	____
11. Do you get any skin symptoms from wearing copper bracelets or other metal objects (such as gold and silver watches, rings, jewelry etc.?)	____	____	____
12.(Women) Are symptoms worse the week *before* your menstrual period?	____	____	____

13. On most days, do you usually feel:
    - ❑ **well or fairly well** , no severe symptoms; able to do all normal work/housework.
    - ❑ **mildly ill**, few if any severe symptoms; able to do almost all normal work/housework.
    - ❑ **moderately ill,** some severe symptoms; able to do some work/housework with limitations.
    - ❑ **very ill** with many severe symptoms, unable to do normal work/housework.
14. On the day of your blood testing, before going to get your blood drawn, were your symptoms:
    ❑ **worse than usual** ❑ **same as usual** ❑ **not as bad as usual**
15. On the day of your urine and stool collection, were your symptoms:
    ❑ **worse than usual** ❑ **same as usual** ❑ **not as bad as usual**

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