Multiple Chemical Sensitivity Syndrome: A Clinical Perspective

I. Case Definition, Theories of Pathogenesis, and Research Needs

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Multiple chemical sensitivity syndrome (MCS) does not appear to fit established principles of toxicology. Yet social, political, and economic forces are demanding that MCS be defined medically, even though to date scientific studies have not identified pathogenic mechanisms for the condition or any objective diagnostic criteria. Consequently, a working definition of MCS can rely only on an individual's subjective symptoms of distress and attribution to environmental exposures rather than currently measurable objective evidence of disease. Nevertheless, patients labeled with MCS are clearly distressed and many are functionally disabled. In this review, four theories of causation are explored: (1) MCS is a purely biologic/physical or psychophysiologic reaction to low-level chemical exposures. (2) MCS symptoms may be elicited by low-level environmental chemical exposures, but the sensitivity is initiated by psychologic stress. (3) MCS is a misdiagnosis and chemical exposure is not the cause. The symptoms may be due to misdiagnosed physical or psychologic illness. (4) MCS is an illness belief system manifest by culturally shaped illness behavior. Areas for further research regarding the etiologies of MCS are suggested. Recognizing that the cause of the syndrome may be multifactorial, strategies are proposed for clinical evaluation and management in Part II of this manuscript using a biopsychosocial model of illness.

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Multiple chemical sensitivity syndrome (MCS) has become a diagnosis increasingly assigned to patients with a variety of commonly experienced symptoms attributed to exposure to various environmental chemicals. In the last decade or so investigators have begun to take seriously the possibility of hypersensitivity to chemical exposures at very low doses.

There are significant ways in which the recognition of MCS as an occupational or environmental illness may interfere with the objective study of this phenomena as a clinical condition.[1] Recognition of this syndrome as an illness, with potential to cause permanent disability, could involve changes in health care coverage and delivery, awarding of workers' compensation benefits, and the regulation of chemicals in the workplace and the environment in the United States. There are social implications related to the increasing human and economic cost of disability in this country. In the vacuum created by the paucity of scientific medical data, MCS is rapidly becoming a politically defined illness.

This paper will discuss various theories of pathogenesis of MCS and areas requiring further research. Recommendations regarding the clinical evaluation and treatment of MCS patients will be discussed in Part II.

To distinguish persons given a diagnosis of MCS from those reporting similar symptoms (such as fatigue, malaise, headache, dizziness, lack of concentration, memory loss, and "spaciness") but labeled with other diagnoses such as chronic fatigue syndrome, an attempt has been made to define MCS in terms of attribution of

symptoms to environmental exposures.

Case Definition of MCS

Cullen's[2] effort to define MCS, primarily for research purposes, is now the most widely used clinical definition for this condition. Objective physiologic or pathologic correlates have not been established. This case definition, if used precisely as stated, allows physicians to distinguish MCS from other collections of similar, commonly experienced symptoms. This definition relies on four salient characteristics: "(1) MCS is *acquired* in relation to some documentable environmental exposure that may initially have produced a demonstrable toxic effect. This aspect excludes patients with long-standing health problems who later attribute certain symptoms to chemical exposure. (2) Symptoms involve more than one organ system, and recur and abate in response to *predictable* environmental stimuli. (3) Symptoms are elicited by exposures to chemicals that are *demonstrable* but very low. The exposures eliciting symptoms may be several standard deviations below the average exposures known to cause toxic or irritant health effects in humans, and typically involve chemicals of widely varied structural classes and different mechanisms of toxicologic action. (4) The manifestations of MCS are *subjective.* No widely available test of organ system function can explain symptoms, and there is no objective evidence of organ system damage or dysfunction."[2]

Despite the absence of "objective" findings of disease to explain symptoms in patients diagnosed with MCS, *the syndrome may be severely distressing and functionally disabling*, even as patients increasingly avoid universally present chemical exposures.

Cullen's case definition[2] does not apply to all patients currently diagnosed with MCS. A definition also was provided by the Ontario Ministry of Health[3] to describe environmental illness, a diagnostic label often used by clinicians synonymously with MCS. Patients "react adversely to some chemicals and to environmental agents . . . , at levels generally tolerated by the majority."

A major practical limitation of Cullen's definition of MCS, and others' definitions of MCS and environmental illness, is the subjectivity and nonspecificity of the available information regarding the "predictable" and "demonstrable" attributes of the exposure-symptom relationship. Whereas these data might be most meaningfully established by double-blinded and controlled exposure challenge testing, they are usually characterized solely on the basis of the patient's report.

To study MCS rigorously, it must be distinguished from objectively defined illness and injury diagnoses, such as contact dermatitis and allergic alveolitis. In these conditions, objective findings are present during active disease, and the causal relationship of those findings to environmental exposure is more readily established. In clinical practice, however, there may be some confusion between acute and chronic occupational or environmental illnesses associated with objective signs of disease and MCS; some patients may have both.

Theories of Etiology of MCS

A broad spectrum of persons may be diagnosed with MCS. Because most physicians see only a few of these patients, who are quite heterogeneous, caution is recommended in generalizing experience with one patient to others with this diagnosis.

There are four major views about the etiology of this syndrome, although more than one of these proposed mechanisms are likely to be operating in different patients and there is some overlap among the views of pathogenesis. One view is that MCS is a physical or psychophysiologic reaction to multiple environmental chemicals. A second view is that MCS symptoms may be precipitated by low-level environmental chemical exposures, but the underlying increased sensitivity is initiated primarily by psychologic stress. A third view is that MCS is a misdiagnosis, and chemical exposure is not the cause of the symptoms. In this case the symptoms may be due to misdiagnosed physical or psychologic illness. The fourth view is that MCS is simply a belief system instilled by certain practitioners, the media, or others in society; MCS is therefore the manifestation of culturally shaped illness behavior.

Physical and Psychophysiologic Mechanisms

MCS, by definition, occurs in response to chemical exposure; the mechanism of causation remains controversial. Proposed causal mechanisms include immunologic injury, neurotoxicity, and behavioral conditioning involving psychophysiologic mechanisms. Theories of psychophysiologic mechanisms for MCS are included in this section because although the symptoms of illness may resemble psychological disorders, the pathogenesis is proposed to be biologic or physical.

The concept of "allergy" has been invoked as a rationale for why MCS patients experience symptoms on exposure to various chemical substances at doses far lower than those associated with objective manifestations of toxicity in most similarly exposed persons. Physician specialists in "clinical ecology" have developed theories of allergic etiology of environmental illness (defined broadly).[4-7] The practices of the clinical ecologists commonly involve interesting, but scientifically unsubstantiated, concepts of allergy and novel, but equally unproven, approaches to diagnosis and treatment which have been discussed at length in other publications and will not be repeated here.[4-7]

Various immunologic mechanisms for MCS have been postulated based on case reports and clinical laboratory test data.[8-12] Some reports have described alterations in T-cell subsets, elevated or reduced helper/suppressor ratios, low titers of autoantibodies, T-lymphocyte activation, or altered interleukin-1 or interleukin-2 levels in people who report low-level chemical exposures and who may have had various symptoms, but not necessarily MCS.[8-12] Across the case reports, how-

ever, there is no consistent pattern of test abnormalities nor a consistent correlation of the reported findings with either specific chemical exposures or disease due to such exposures.[5,13-16] Also rarely are data presented for control subjects, nor are the control subjects known to be without low-level chemical exposures.

There are many problems with theories implicating a disturbance of the immune system as the cause of MCS. There are inadequate or widely variable reference ranges for many of the tests used; several lack accepted and standardized laboratory protocols. Immune parameters may fluctuate up and down with exposure to infectious agents, hormones, or environmental stressors. The published research often has been performed by persons associated with commercial laboratories; other investigators generally have failed to replicate the reported findings.[5,13-16]

In an outbreak of illness in aerospace workers reported by Sparks and colleagues,[13] a number of the workers had been evaluated with such immunologic tests performed by one commercial laboratory. Retesting in a university-based immunology research laboratory showed that the previously reported IgE and IgG antibodies to formaldehyde were not detectable.[13,16] Immunologic variables were measured by the same commercial laboratory in Simon and colleagues' controlled and blinded study of MCS clinic patients and control subjects selected from a musculoskeletal clinic population.[14] There were no significant differences between case and control subjects in the prevalence of "positive" antitissue, autoimmune antibodies or antichemical antibodies. There were also no significant differences between groups in the average number of T-cell lymphocyte subsets (including TA1 cells) or the generation of interleukin-1 by in vitro cultured monocytes (Table 1). Immunologic assays generally have shown limited reproducibility during submission of duplicate samples, suggesting methodologic problems as well.[14] The one controlled and blinded cross-sectional evaluation of immune parameters in MCS patients that currently exists in the medical literature revealed no consistent pattern of abnormalities.

TABLE 1
Comparison of Immunologic Studies in Patients with Multiple Chemical Sensitivity and Control Subjects with Musculoskeletal Injury[14]

Immunologic Study	Case Subjects (n = 41)	Control Subjects (n = 34)	95% CI for Difference*	P
Positive test for autoantibodies, n (%)				
Antismooth muscle	20 (49)	16 (47)	−0.22 to 0.24	.2
Antiparietal cell	4 (10)	4 (12)	−0.16 to 0.12	>.2
Antibrush border	5 (12)	11 (32)	−0.02 to −0.40	.03
Antimitochondria	1 (2)	0 (0)	−0.06 to 0.02	>.2
Antinuclear	4 (10)	2 (6)	−0.04 to 0.22	>.2
Any positive	26 (63)	23 (68)	−0.28 to 0.14	>.2
Cellular studies (±SD)				
Lymphocyte count, $\times 10^3$/liter	2580 (±546)	2450 (±778)	−171 to 431	>.2
B cells, % (±SD)	6.4 (±4.1)	7.4 (±6.3)	−1.4 to 3.8	>.2
T cells, % (±SD)	69.8 (±9.7)	67.4 (±7.9)	−1.6 to 6.4	>.2
CD4+ helper series, % (±SD)	49.4 (±9.2)	46.1 (±7.1)	−0.5 to 7.1	.1
CD8+ suppressor cells, % (±SD)	23.2 (±7.7)	22.5 (±7.4)	−2.8 to 4.2	>.2
Interleukin-2+ cells, % (SD)	2.1 (±2.0)	2.1 (±2.2)	NA†	>.2
TA1+ cells, % (±SD)	6.5 (±5.5)	13.0 (±10.4)	NA†	.008†
Interleukin-1 generation	3.9 (±5.02)	7.72 (±6.09)	NA†	.003†

* 95% confidence interval (CI) given in same units as original measure (proportions for serologic measures, percentages for lymphocyte subsets).

† Skewed distribution requires use of Wilcoxon test; confidence intervals not calculated. NA, not available.

No controlled and blinded challenge studies have been published demonstrating a consistent pattern of alteration in immune parameters in MCS patients after chemical exposure with the patient serving as his or her own control.

Another hypothesis is that MCS results from inflammatory mediators released by cell membranes. This process is thought to be initiated by toxic free radicals produced by offending chemical exposures. Vulnerability to MCS is thought to be due to a deficiency of antioxidants.[17] There are few or no scientific data available to examine this theory.

Other investigators have postulated that MCS is related to altered function of the respiratory mucosa through amplification of the nonspecific immune response to low-level irritants.[18,19] It is postulated that this might be mediated through c-fiber neurons and the release by the airway epithelium of cytokines producing an acute local inflammatory response, or altered neuroepithelial interaction. Sensory c fibers may serve as both afferent and efferent nerves for neurogenic inflammation triggered by environmental irritants and may release various mediators, such substance P, capable of producing vasodilation, edema, and other manifestations of inflammation.[19] Substance P is degraded by neutral endopeptidase, the action of which is inhibited by environmental irritants such as cigarette smoke.[19] It is postulated that depletion of neutral endopeptidase or other enzymes by irritant exposure might amplify the response to exposure to other irritants.[19]

Studies of exposure to the organic vapor phase of environmental tobacco smoke in rats have demonstrated vascular extravasation thought to occur from irritant stimulation of the c-fiber neurons.[20] Vascular congestion may be the mechanism of increased nasal resistance observed in human subjects with self-reported sensitivity to environmental tobacco smoke when challenged with brief, high levels of tobacco smoke.[21] Also, an increase in baseline nasal resistance and in re-

sponse to odors has been observed in patients with MCS when compared with control subjects.[22]

Meggs and Cleveland[23] described findings of edema, excessive mucus, a cobblestone appearance of the posterior pharynx and base of the tongue, focal areas of blanched mucosa, and mucosal injection in 10 MCS patients who underwent rhinolaryngoscopy. They have proposed use of the term "reactive upper airways dysfunction syndrome" to describe persons who report persistent chronic rhinitis and increased sensitivity to odors following an acute irritant chemical exposure.[23] Koren et al[24] have reported an increase in polymorphonuclear cells in nasal lavage fluid from *asymptomatic* subjects after exposure to a volatile organic compound mixture typical of that found in indoor air. No controlled studies have demonstrated a greater prevalence of objective parameters of upper airway inflammation in MCS patients.

Neurogenic inflammation of the upper respiratory tract does not appear to account for all the multiorgan system complaints in MCS patients but might help explain some of them. It is possible for local inflammation to be associated with systemic symptoms, such as the fatigue and myalgia associated with viral infection of the upper respiratory tract. Mediators of inflammation, such as interleukins, may be released from the site of inflammation and affect distant sites.[19] Also, in animals, nasal irritation has been demonstrated to activate systemic reflexes producing increased blood pressure and bradycardia,[25] although this has not been studied in MCS patients.

Other than Doty's nonspecific finding of increased nasal resistance,[22] no controlled biopsy or lavage studies, objective finding of respiratory mucosal inflammation, or evidence of activation of nonspecific immune mechanisms in MCS patients have been published. However, the theory of this phenomenon appears testable with currently available research tools.

In most studies, a disproportionate number of patients with MCS are women (Table 2).[2,5] It is possible that women have a different physiologic response to low-level chemical exposure than do men. Most studies of the health effects of occupational exposure to chemicals have involved men primarily, and may not be readily applicable to MCS. It has been noted that women have a lower threshold for the perception of odor than do men.[22,26] However, Doty et al[22] reported that a lowered olfactory threshold was not more common in MCS patients than in control subjects. Other physiologic and/or hormonal gender differences have not been studied in humans as they may relate to the MCS phenomenon.

Some investigators have proposed a behavioral conditioned response to odor,[27] in which a strong-smelling, chemical irritant causes a direct and nonconditioned physical or psychophysiologic response. Later, the same odor at a much lower concentration causes a conditioned response of the same symptoms. Through stimulus generalization, different odors or irritants become the precipitant for similar symptoms. "Clinical experience" of several of the authors indicates that this mechanism is likely to occur in some MCS patients, although this has not been demonstrated experimentally in humans. It remains to be seen how this mechanism applies to MCS, wherein multiple chemicals with different odors or irritant properties trigger symptoms.

Another currently popular theory of causation of MCS proposes a biologic mechanism for the conditioning model described above. This theory proposes that exposure to odors and respiratory irritants may precipitate physiologic and psychological symptoms, due perhaps to interactions between the nervous and endocrine systems.[26,28-31] There are different anatomic links between the olfactory nerve, the "limbic system" (including portions of the hippocampus, amygdala, cingulate, and subcallosal gyri) and the hypothalamus, which govern the parasympathetic and sympathetic nervous systems. It is postulated that these rich neural interconnections may explain how odor or low-level irritation of the respiratory tract indirectly produces symptoms referable to multiple organ systems.

Bell and colleagues[26] point out that rodent studies[32] have demonstrated that single high-level or intermittent, repeated low-level environmental chemical exposures cause limbic "kindling" (eg, the ability of a repeated, intermittent electrical or chemical stimulus that is initially incapable of producing a response to eventually induce seizure activity in later applications). In cats, partial kindling has been demonstrated to result in affective behavioral changes without seizures,[32,33] whereas primates are more likely to demonstrate partial complex seizures in response to electrical kindling.[34] Animal studies also demonstrate time-dependent sensitization, or amplification of subsequent responses to a chemical or novel and threatening psychological stimulus, by the passage of time between stimuli.[35]

Kindling and time-dependent sensitization also have been postulated to explain the initiation of psychiatric disorders such as depression[36] and posttraumatic stress disorder[37] in some persons, independently of the MCS phenomenon.

Bell and colleagues[26] suggest that subconvulsive chemical kindling of the olfactory bulb, amygdala, piriform cortex, and hippocampus, as well as time-dependent sensitization, are central nervous system mechanisms that could amplify reactivity and lower the threshold of response to low levels of inhaled chemicals and could initiate persistent affective, cognitive, and somatic symptomatology in some vulnerable persons who may be genetically predisposed to affective spectrum disorders.[26] They postulate that

TABLE 2
Demographics of MCS and Environmental Illness

Study Population (Ref)	% Women (n)
Black et al[55]	88 (23)
Terr[4]	70 (63)
Simon et al[58]	85 (11)
Simon et al[14]	85 (41)

this neurologic sensitization might occur with either a single, high-dose exposure to a chemical substance, followed by much smaller subtoxic levels of exposure to the same chemical, or with repeated lower dose exposures, as has been demonstrated in animals.[26] It has been observed that time-dependent sensitization occurs more readily in female rats,[38] which is postulated to have relevance to the apparent preponderance of females among MCS patients.[26]

There are, however, no experimental data in humans to support or refute the role of chemically induced kindling or time-dependent sensitization in producing MCS, or to determine whether the proposed mechanisms, if verified experimentally, would be specific to MCS patients. In addition, kindling occurs in animals in response to pharmacologically effective doses of drugs or other chemical substances rather than trace exposures. Thus, if this mechanism is at work in MCS patients, one might expect a higher prevalence of MCS in solvent abusers who intermittently sniff large amounts of solvent-containing glue, for example, but available information does not suggest that this is the case.

There are small case series reports in which organic solvents[27,29,30] or cocaine[39] have precipitated panic attacks. Schusterman and Dager[40] have proposed the descriptive designation of "odor-triggered panic attacks or panic disorder" for cases in which one or more chemical odors trigger either typical or limited panic attacks. They postulate that odor produces annoyance and autonomic arousal, which then may be amplified in a person with predisposing cognitive, personality, or biologic susceptibility. A supportive finding of autonomic arousal in response to odor (increased heart and respiratory rate) is described by Doty et al[22] in MCS patients.

Although there are limited data to support this contention, low-level exposure to irritants or odors may produce psychophysiologic symptoms that, in some vulnerable persons, may evolve into MCS. Psychophysiologic symptoms occurred with very high prevalence in the group of aerospace workers evaluated by Sparks and colleagues,[13] most of whom had no significant histories of psychiatric illness (Table 3). The exposures to organic solvents and other chemicals were several standard deviations below the levels reported to be associated with toxic or irritant effects. Follow-up information on almost all the workers evaluated in this outbreak indicated that most workers experienced improvement in symptoms after removal of the offending chemical odor/irritant (phenol-formaldehyde composite material) from the plant, suggesting that some of the prevalent symptoms of depression and anxiety might have been induced by exposure to this material[41] (although other contributing factors were clearly operant in this situation).

Some researchers have noted persistent alterations in quantitative electroencephalogram (EEG), evoked potentials, or brain electrical activity mapping in animals and humans with both high-dose and repetitive lower dose exposure to pesticides or other chemical substances.[42] Others have noted acute changes in EEG patterns after exposure to odors, even at levels of exposure that were undetected consciously.[43]

Selner and Staudenmayer[44] found that persons with chemical sensitivities resembled patients being treated for various psychological conditions, rather than control subjects without illness, with regard to the distribution of subjects across eight categories of slow-wave EEG spectral patterns associated with attentional deficits. This could suggest either that MCS patients have primary psychiatric conditions or that they may resemble patients with psychologic conditions induced by chemical exposure. Also, the increased beta activity noted on the EEGs of chemically sensitive patients is not specific to psychologic disorders, and other explanations for these nonspecific findings are plausible.

No controlled and blinded studies have examined MCS patients exposed to various chemical substances to look for acute reproducible alterations of brain electrical activity.

Bell and colleagues[26] suggest that a history of cacosmia (a subjective sense of altered olfactory function and feeling ill on exposure to chemical odors, although not necessarily meeting the case definition for MCS) might be associated with neurocognitive dysfunction, based in part by a study of cacosmic solvent-exposed workers by Ryan et al.[45] Simon and others[14] found that MCS patients differed little from control subjects on selected measures of neurocognitive function. There are no data that MCS patients demonstrate a consistent or specific pattern of neurocognitive deficits, at least in cross-sectional studies, and disturbances of memory and attention observed in some MCS patients may be a result of depression and/or anxiety. There are no studies examining neurocognitive deficits with controlled and blinded chemical exposures at low levels (with the subject serving as his or her own control) to assess acute and reversible changes in neurocognitive function, but this may be feasible to do in the future.

One argument against physical toxic injury as a cause of symptoms in MCS patients is the observation that many MCS patients attribute their symptoms to environmental chemical exposures (in the office environment, for example) that are many orders of magnitude below those of other workers in manufactur-

TABLE 3
Summary of Neuropsychiatric Findings in 53 Aerospace Workers with Workplace Chemical Exposures[13]

Findings	Subjects	
	Number	%
Current depression	32	60
Past depression	12	23
Current panic disorder	14	26
Current panic attacks	3	6
Past panic disorder	2	4
Somatization disorder	3	6
Somatization trait	14	26
Abnormal findings on Mini-Mental State examination*	4	8

*The Mini-Mental State examination is part of the National Institute of Mental Health's Diagnostic Interview Schedule.

ing jobs.[28] Better information must be obtained regarding the prevalence of MCS in various populations to affirm or refute this preliminary observation that suggests that the intensity of exposure to various chemical exposures does not match the prevalence of MCS symptoms.

The relationship of MCS symptoms to environmental chemical exposures also does not appear to fit other established principles of toxicology. There is agreement among occupational health professionals that any natural or synthetic chemical exposure in sufficient doses may be harmful to specific organs of the body and can produce objectively measurable toxic effects.[46,47] Causal relationships between toxic exposures and human disease generally are established by determining the strength of the association between exposure and the development of disease using epidemiologic methods and toxicologic animal models, dose-response relationships, and the consistency and predictability of the clinical responses to specific chemical exposures in affected human subjects.[47] In MCS, all of these criteria are currently lacking.

Even if it is assumed that alterations in olfactory-limbic-temporal or other central neurophysiologic functions is one mechanism of symptom induction in patients with MCS, the pathophysiologic significance of such alterations is far from clear. Central neurophysiologic alterations consequent to exogenous chemical exposures might represent toxic injury or perhaps a maladaptive but reversible central nervous system response pattern, ie, a form of behavioral conditioning. The treatment and lifestyle implications of these alternative response patterns are contradictory because chemically induced injury would probably preclude further exposure to the suspect chemicals and would justify some physicians' recommendations for chemical avoidance. However, the latter response pattern might be amenable to readaptation through behavioral, cognitive, environmental, or even pharmacologic interventions, with the goal of progressive resumption of normal activity.

MCS as a Manifestation of Stress

Jewett[48] postulates that cacosmia, as well as functionally disabling MCS, may be a manifestation of the human response to stress. Whatever the initial precipitating event (whether it be psychologic, loss of self-esteem, fear of harm from chemical exposure, or other physical illness), the person experiencing stress may exhibit heightened sensitivity to odors or respiratory tract irritants. In most people, cacosmia does not lead to major lifestyle changes or functional disability. A small percent, however, may develop MCS.

This theory receives some support from an animal study that revealed that one brief exposure to a psychologic stressor induced long-lasting, time-dependent sensitization to certain drugs.[35] Bell et al[26,49] have postulated that the time-dependent sensitization phenomenon described in the previous section may be produced by either chemical exposures or psychologic stressors in humans, resulting in future cross-reactivity to both chemical exposures and psychologic stressors.

Bell et al performed a questionnaire survey of college students[49] and community elderly volunteers participating in a longitudinal survey of bone density at a local hospital.[50] Extreme cacosmia was defined as a self-report of feeling ill on exposure to four or more of the following chemicals: pesticides, automobile exhaust, paint, new carpet, or perfume. Both surveys revealed a fairly high prevalence of extreme cacosmia to multiple odors (15% and 17%, respectively). The extremely cacosmic group included significantly more women than men among college students but not among the elderly. The extremely cacosmic subgroup of college students had higher anxiety and depression rating scores than did students who reported a lower degree of cacosmia. The extremely cacosmic elderly respondents reported higher ratings for anxiety and recent major life changes, but not depression. These findings support the theory that psychologic stress may play a role in a person's subjective sensitivity to odors from chemical exposure. The reporting of symptoms in response to odors could also simply be a reflection of the increased tendency of depressed and anxious persons to report symptoms of any kind. Less than 1% of the extremely cacosmic college students and 9% of the extremely cacosmic elderly reported physician-diagnosed MCS, and none of the noncacosmic subjects had this diagnosis.

It is unknown, however, whether persons with marked cacosmia are more likely to present to physicians with the clinical syndrome of MCS, but this would be interesting to study prospectively in college students, for example, most of whom are not likely to have developed cacosmia due to a chemical spill or repetitive occupational exposure to chemicals.

MCS as Other Misdiagnosed Illnesses

It has been suggested that MCS is a misdiagnosis and chemical exposure is not the cause of the symptoms. In contrast, the patient's complaints may be due to a misdiagnosed physical or psychological illness. The likelihood of misdiagnosis may be furthered by conscious or subconscious attempts by the patient or physician to avoid a psychiatric diagnosis.[4,51-55]

Some investigators have concluded that many, if not most, MCS patients are not significantly different from psychiatric patients who do not project their disorder and distress onto the environment.[4,5,51-55] They argue that the available studies indicate that MCS is not a distinctive diagnostic category and that the label is incorrectly applied to many patients who otherwise meet criteria for depression, anxiety disorders, somatization disorder, and other common psychiatric disorders.[4,5,40,51-58] In situations where a history of chemical exposure is obtained, the clinical ecologist or other physician may misinterpret symptoms of common psychiatric disorders as indicating the patient has MCS. Published case series (with varying case definitions) have reported an increased frequency of symptoms ca-

tegorizable as depression, anxiety disorders, somatization, obsessive-compulsive disorder, and other personality disorders in persons diagnosed with MCS, as well as greater frequency of abnormal elevations on various subscales of the Minnesota Multiphasic Personality Inventory (Table 4).[4, 5, 54-59]

The explanation that primary or misdiagnosed psychiatric disease may be the actual cause of MCS has been based largely on clinical experience lacking standardized case definitions, examiner blinding, and appropriate comparison groups. Some controlled studies, however, have yielded findings that demonstrate the importance of psychologic mechanisms in the manifestation, if not the etiology of MCS in many people with the syndrome.

Because of the possibility that MCS itself might produce psychiatric symptoms, some investigators have tried to evaluate the presence of preexisting symptoms of psychiatric illness in patients diagnosed with MCS.[14, 58]

Among the group of aerospace plastics workers evaluated by Sparks and others,[13] there was a subgroup of 13 who fit a case definition of MCS similar to Cullen's and who also had a history of decreased functional status due to their symptoms. These workers were compared with an unmatched group of symptomatic coworkers with similar exposures but without MCS.[58] Thirty-seven symptomatic workers completed structured diagnostic interviews and self-report measures of somatization and psychopathology.

The 13 workers with MCS scored significantly higher on measures of preexisting somatization and psychopathology than did the other workers.[58] The greatest differences were noted in histories of anxiety, depressive disorders, and somatization. A history of somatization and psychiatric morbidity predating workplace exposure to chemicals was the strongest predictor of MCS (although it should be noted that six of the MCS subjects gave no history of a diagnosis of anxiety or depression). The finding of a higher lifetime burden of psychiatric illness is consistent with previous findings for conditions such as fibromyalgia, chronic fatigue syndrome, and chronic pelvic pain.[60-63] It was postulated that a nonspecific precipitating event that is perceived by a person as harmful or causing unusual stress could result in continuing symptoms and disability in vulnerable persons even though no specific or measurable toxicologic injury occurred.[58, 64] This study[58] was limited by nonblind assessments and the bias inherent in studying persons involved with workers' compensation claims. Furthermore, the findings did not exclude the possibility that those with MCS may have experienced odor-triggered panic attacks or other psychophysiologic symptoms on exposure to low-level respiratory tract irritant chemicals.

Fiedler et al[65] presented findings on a case series of 11 subjects who met Cullen's criteria for MCS and who had no history of mental health treatment. The absence of prior psychiatric diagnosis and treatment was based on the patient's current reporting, not verified by review of previous medical records. The study attempted to demonstrate that MCS could exist in the absence of preexisting or coexisting psychiatric disorders or misdiagnosed physical conditions. Structured interviews confirmed a lack of symptoms consistent with preexisting psychiatric disorders, including somatization, although it was noted that four (36.4%) patients currently met *Diagnostic and Statistical Manual*, 3rd edition, revised (DSM-III-R) criteria for major depression and six (54.5%) had Minnesota Multiphasic Personality Inventory scores characteristic of somatization. Fiedler et al[65] also noted that the subjects had very high scores on measures of psychosocial distress. This study could not determine whether the symptoms of depression and anxiety were due to chemical exposure, some as-yet-undefined physical condition associated with MCS, or arose de novo and were simply attributed retrospectively and mistakenly to chemical exposure.

Terr[4] found that the medical records of 90 patients diagnosed as having work-related MCS and engaged in workers' compensation litigation contained documented evidence of the same multiple symptoms for many years before the employment of concern in 56 (62%) of the cases.

TABLE 4
Environmental Illness and Misdiagnosis[59]: Review of Eight Case Series of Environmentally Ill Subjects

Investigator (Ref)	Year Published	Location	N	Mean age, y (range)	% Female	% with Psychiatric Symptoms*
Brodsky[66]	1983	San Francisco	8	30 to "early 50's"	88	100
Pearson, et al.	1984	Manchester, Eng	19	39.1	68	95
Stewart and Ruskin[52]	1985	Montreal	18	38	83	100
Terr[5]†	1986	San Francisco	50	38.5	78	–
Terr[4]†	1989	San Francisco	90	39.5 (20–63)	70	42
Simon et al[58]	1990	Seattle	13	–	–	92
Black et al[55,56]	1990/1993	Iowa City	26	49.1 (27–78)	88	87‡
Fiedler et al[65]	1992	Piscataway, NJ	11	42, men; 43, women (28–57)	73	72

* Different methods were used to determine psychiatric symptoms, but were counted if they yielded a definite diagnosis, or significantly abnormal ratings on self-report assessments, such as the Minnesota Multiphasic Personality Inventory.

† Overlapping data sets.

‡ Only 23 of 26 were assessed for psychiatric symptoms.

Black et al[55,56] compared 26 subjects recruited from a community and clinic population with environmental illness (defined broadly and not necessarily meeting Cullen's definition of MCS) with 46 age- and sex-matched general population control subjects. Twenty-three were given standardized psychiatric assessments including the Diagnostic Interview Schedule and the Structured Interview for DSM-III-R Personality Disorders. Several self-report instruments were used to assess somatic concerns, hypochondriacal behavior, and past and current major depression. Sixty-five percent of assessed subjects met criteria for mood, anxiety, or somatoform disorders compared with 28% of the control subjects, a significant difference. Nearly three-quarters of the subjects met criteria for at least one personality disorder, compared with 28.3% of control subjects, also a statistically significant difference. Only 3 of the 23 subjects assessed were free of a major mental or personality disorder, certainly a higher prevalence than community control subjects. The authors concluded that most patients diagnosed with environmental illness have unrecognized emotional problems that were not being appropriately diagnosed and treated.[55,56,59]

In regard to the foregoing discussion, it should be noted that without necessary modification, the structured Diagnostic Interview Schedule interview protocol has no ability to distinguish whether so-labeled "past" psychiatric morbidity actually predated the onset of the illness under study or whether "current" psychiatric morbidity was not present before the current illness. In addition, the use of a community rather than a clinic control group may have contributed to the observed difference in morbidity, given the generally lower prevalence of psychologic symptoms and disorders within the general community. However, despite these limitations, it was clear that these subjects suffered substantial psychiatric and emotional morbidity, although etiology could not be determined.

A recent study by Simon and colleagues[14] evaluated psychologic and other parameters in MCS and included case and control groups from two defined clinic populations. Psychiatric assessment was performed using self-report measures and structured interviews, but including modifications to contrast dates of onset of any diagnosable psychologic disorders and the study condition.[14] Again, there was a greater prevalence of symptoms consistent with depression, anxiety, and somatization in MCS case subjects than in control subjects, who were patients from a musculoskeletal clinic without evidence of systemic disease (Table 5).

In particular, although there was no apparent difference in the prevalence of preexisting anxiety or depression, the prevalence of somatization symptom pattern among MCS patients *before* the onset of MCS was significantly greater than in matched control subjects.[14] While acknowledging that retrospective assessment has limited ability to discern temporal patterns of disease, the authors postulated that, among a substantial proportion of persons who develop MCS, preexisting psychologic vulnerability plays a significant role in their development of the syndrome. It is also noteworthy that in this study about half of the MCS cases did *not* meet diagnostic criteria for any psychiatric illness, and 25% also had levels of psychiatric symptom reporting that were well within "normal" community reference standards.[14]

In the above studies[14,55] most of the subjects and comparison groups were women, suggesting that gender differences in the prevalence of depression and anxiety disorders do not account for the higher prevalence of psychiatric diagnoses in MCS patients.

Bell et al[26] and others argue that (1) DSM-III-R diagnoses are simply a collection of symptoms and do not define etiology, (2) identifying affective disorders in persons diagnosed with MCS does not establish their etiologic role nor does it rule out other concomitant illnesses, and (3) the observation that psychiatric treatments improve symptoms in some (but not most or all)

TABLE 5
Comparison of Psychologic Studies in Patients with Multiple Chemical Sensitivity and Control Subjects with Musculoskeletal Injury[14]

Psychological Study Result	Case Subjects (n = 41)	Control Subjects (n = 34)	95% CI for Difference*	P
SCL-90 symptom scores, mean raw scores (±SD)†				
Depression	1.19 (±0.91)	0.51 (±0.44)	0.32 to 1.04	<.001
Anxiety	0.87 (±0.89)	0.29 (±0.36)	0.30 to 0.89	.001
Somatitization	1.30 (±0.74)	0.64 (±0.49)	0.37 to 0.94	<.001
Current structured interview diagnoses, n (%)				
Panic disorder	10 (24)	1 (3)	0.07 to 0.35	.008
Generalized anxiety	4 (10)	0 (0)	0.01 to 0.19	.06
Major depression	12 (29)	4 (12)	0.0 to 0.34	.08
Any of the above	18 (44)	5 (15)	0.1 to 0.48	.006
Structured interview somatization symptom count, mean (±SD)‡	15.5 (±5.9)	3.5 (±2.8)	10 to 14	<.001
Preexisting structured interview diagnosis, n (%)				
Panic disorder	3 (9)	5 (15)	−0.09 to 0.21	>.2
Generalized anxiety	2 (6)	4 (12)	−0.02 to 0.14	>.2
Major depression	16 (47)	10 (29)	−0.04 to 0.40	.1
Any of the above	16 (47)	12 (35)	−0.10 to 0.32	>.2
Structured interview somatization symptom count, mean (±SD)	7.9 (±7.1)	2.4 (±2.6)	3.2 to 7.8	<.001

* 95% confidence interval (CI) given in same units as original measure (proportions for diagnostic measures, symptom counts for somatization measures).

† Mean scores in general population samples were approximately 0.3 for women and 0.2 for men (23), with a higher score indicating more distress.

‡ Mean scores in general population samples are approximately 2.0 (28).

¶ SCL, Symptom Check List.

patients with MCS does not rule out neurotoxic or other causal mechanisms.

Even in the studies reporting an excess of psychiatric illness in MCS subjects,[14,55,58,65] there is a relatively small proportion of persons diagnosed with MCS who do not have histories of preexisting (or concurrent) psychiatric disorders or abnormal elevations on self-report measures of psychologic distress predating exposures of concern. This group might be an interesting population in which to study the effect of chemical exposure on clearly defined health parameters, but it may not be representative of other MCS patients.

Finally, the finding of a higher prevalence of current psychiatric disorders in MCS patients does not exclude the possibility that those with MCS experienced odor-triggered panic attacks or other psychophysiologic symptoms on exposure to low-level respiratory tract irritants as the precipitating event for their illness.[41] It also does not exclude the possibility that chemical exposure, or fear of harm from chemical exposure, was the precipitating event for the onset of symptoms of MCS in persons with preexisting psychologic symptoms or vulnerability.

MCS as an Illness Belief System

Other professionals have postulated that in many ways MCS is a belief system.[53,59,66] Promoted by clinical ecologists and those sympathetic to their views, and followed by medically unsophisticated laypersons, the belief is reinforced by referring patients to a network of similarly minded clinicians, and establishing support groups, hotlines, journals, and clinics to support and reinforce these beliefs. Some have called this phenomenon a medical subculture.[66] According to this model, the group psychosocial dynamic among patients diagnosed with MCS facilitates and perpetuates rationalizations regarding the role of external and uncontrollable factors in their illness, rejects the concept that symptoms are not indicative of severe disease or may have psychologic components, and promotes the assumption of the patient as a victim, associated with assertive or adversarial interactions with conventional health care and disability systems.[4,51]

It has been observed that MCS shares many features with other diagnostic categories, such as chronic fatigue syndrome, fibromyalgia, neurasthenia, or chronic postviral syndrome, that encompass persons with distress and functional disability characterized by few or no objective findings. It has been speculated that MCS is simply the most contemporary cultural expression of psychosomatic illness.[51,53,66]

Shorter,[67] a sociologist and historian, chronicles the connection between psychologic distress and its expression as shaped by the patient's interaction with the physician and the prevailing culture. He observes, that in the 19th century, motor signs were the most common manifestation of this distress and were then medically irrefutable, whereas the somatic expressions of psychogenic illness in the 20th century have shifted to more subjective symptoms such as pain and fatigue. This shift was concurrent with improvement in the ability to diagnose neurologic disease by objective testing. Subjective symptoms of headache and fatigue remain difficult to "disprove" by available diagnostic methods. He theorizes that the "psyche does not wish to be revealed," therefore, there is a shift to untestable symptoms.[67]

Shorter[67] suggests that a set of psychosomatic symptoms becomes attached to a disease label in phases. The first involves the establishment of parallels between common symptoms and conventionally accepted organic diseases. Conditions popularly believed to be difficult to detect or substantiate, and which are thought to have a cause of origin external to the patient, such as neuropsychiatric manifestations of chronic solvent intoxication or immunologically mediated allergy, provide a template or point of reference. Subsequently, sympathetic physicians, patient support and advocacy groups, and the media publicize the presumed etiologic association. Eventually this may result in an increase in symptom attribution, rather than an increase in actual organic illness.

Physicians play an important role in shaping symptom expression by their patients.[67] Recent popular medical concerns about immune dysfunction or environmental toxicity also may have shaped the expression of symptoms in accordance with what both medical practitioners and society consider "real" illness.

Abbey and Garfinkel[68] note that chronic fatigue syndrome and neurasthenia have many overlapping symptoms, in that neither is a definite syndrome but, rather, they represent explanatory labels for a wide variety of functional somatic symptoms. Similarly, Buchwald and colleagues[69] note the symptom overlap of chronic fatigue syndrome and MCS.

The studies to date indicate that a disproportionate number of sufferers of chronic fatigue syndrome and MCS are women.[2,4,28,69] Women report more symptoms and seek medical care more often than do men.[69] The psychosocial experiences of women are also different than that of men. It has been argued that symptoms labeled with these diagnoses may be manifestations of the mismatch between women's ambitions and social possibilities or women's conflicting roles in modern society.[68]

Another factor that may contribute to culturally shaped illness belief systems regarding health effects of chemical exposure is the increasing concern of the public regarding environmental pollution and health effects of exposure to man-made chemicals.[1] Specialized centers have developed for the evaluation and treatment of persons with health problems suspected to be due to occupational or environmental exposure, along with growth of the academic training of physicians in this specialty area. Employers and manufacturers have been asked to reduce noxious exposures and provide those exposed with detailed information regarding health risks. Patients and their primary care physicians, many of whom obtain their information regarding chemical hazards from the lay press, increasingly regard man-made

chemicals of any kind as unacceptable threats to health.[1,70] Many physicians do not appear to apply accepted principles of pharmacology and toxicology to their assessment of health risk of environmental chemical exposures. For example, 38% of physicians surveyed by McCallum[70] reported the belief that it was not how much of a chemical to which one was exposed that determined health risk but whether one was exposed at all. This atmosphere has led to a highly litigious climate where occupational and environmental health are concerned.[1]

It is highly unlikely that the majority of MCS patients are simulating their symptoms, or that symptoms in most MCS patients result from suggestion or shaping on the part of the culture or their physicians, although the attribution of symptoms to environmental chemical exposure is likely due to suggestion in some cases. It is probable, however, that a patient's beliefs regarding illness modify the expression of symptoms even when resulting as a direct toxic effect of chemical exposure. The illness belief/behavior theory of MCS arises from historical and sociologic evidence and clinical observations but has not been subjected to controlled investigation.

Conclusions Regarding Theories of Etiology

Understanding the phenomenon of MCS requires evaluation of pathophysiologic, psychologic, and social factors using the biopsychosocial model of illness.[64,71] The comprehensive biopsychosocial model is a systems approach that conceptualizes an intimate mind-body connection; physical diseases have psychologic and social correlates, and psychologic illnesses have physical correlates, as in the cases of hypertension and peptic ulcer disease, for example. Illness is an experience whose presence is usually communicated by complaint; physical signs may be present or absent. *Illness should not be regarded as less "real" because of the possibility that psychogenic mechanisms may play a major role in causation for many sufferers.*

The available evidence shows that patients diagnosed with MCS are very heterogeneous, and that more than one causal mechanism may be operative in different cases. It is possible that preexisting or concurrent psychiatric illness, particular health belief models, and psychologic stress may produce a vulnerable group of persons who then develop a sensitivity to odors or low-level chemical irritants that occur as a result of one or more of the above proposed mechanisms. Because none of the above views of etiology of MCS is universally accepted on the basis of substantial scientific evidence, dogmatic adherence to one of them is unwise as a basis for managing individual patients with an MCS diagnosis. Furthermore, one could postulate still other theories or some combination of them. In the face of uncertainty regarding the etiology of symptoms in an individual patient, it is prudent for the clinician not to substitute his or her own beliefs about etiology for the patient's observations. *The fact that there is no agreement upon any one etiology for most patients with MCS does not prevent clinicians from helping affected patients with their symptoms.* An approach to diagnosis and treatment of the MCS patient is discussed in Part II of this report.

An important distinction should be made between the psychophysiologic effects of exposure to odors and respiratory tract irritants, which may occur in both normal persons and those with preexisting psychiatric disorders, and the chronic disability experienced by many patients with MCS, even after control or removal of the offending exposures.[13,41,58] The chronicity of the symptoms of MCS, and the coexisting psychiatric illnesses that are clearly present in many of these patients, should not obscure the observation that exposure to volatile organic compounds, at levels far below those usually associated with central nervous system toxicity, may precipitate psychophysiologic symptoms consistent with panic attacks and depression even in persons without evident coexisting or preexisting psychiatric illness.[13,41,58] Thus, it is *not* appropriate to dismiss psychophysiologic symptoms in response to odors or irritants in all MCS patients as exclusively due to preexisting or coexisting psychiatric illness by concluding that their symptoms are "all in their heads."[41,72]

Research Recommendations

There is an ongoing problem in reliably and distinctively defining MCS for multicenter studies on pathogenesis. Any definition, however, should at a minimum consider circumstances of symptom onset in relationship to some demonstrable chemical exposure, otherwise there will be little to distinguish MCS from other illnesses such as chronic fatigue syndrome, or psychiatric diagnoses such as major depression or somatization disorder. A clear distinction should be made between MCS and other medical diagnoses that may be due to occupational exposure such as allergic rhinitis, contact dermatitis, and acute solvent intoxication.

Uncontrolled and unblinded challenge testing (ie, removal from the offending chemicals and then rechallenge after an appropriate interval, with the outcome of interest being a clearing of symptoms with removal from the offending chemical and recurrence of symptoms upon rechallenge) has no defensible role in research and is too open for misinterpretation to be useful in forming a case definition for MCS either clinically or in research.

Research is needed to determine the actual prevalence and incidence of MCS in various populations as well as changes over time.[1,73]

The various clinical presentations of MCS should be defined clearly because different clusters of causal factors may be operating in each. For research, the definition of MCS must fit the stated aim of the investigation. One that specifically excludes persons with preexisting psychiatric disorders might facilitate the evaluation of MCS patients with regard to the effect of environmental exposure on well-defined clinical outcomes.

Because MCS is expressed subjec-

tively, proper scientific methods are mandatory in the evaluation of outcome measures of the effects of low-level chemical exposure. The use of a specially constructed environmental challenge chamber may be required for double-blinded, placebo-controlled testing of specific outcome measures after low-level chemical exposure.[74] The outcome measures may include subjective responses or objective measures consistent with the person's subjective symptoms. Evaluation of the impact of removal from chemical exposures for a period of time before challenge testing (deadaptation) should also be subject to controlled evaluation.[74]

The theory that neurogenic inflammation plays a prominent role in the pathogenesis of MCS could be tested.[19] This might include the measurement of inflammatory cells and mediators of neurogenic inflammation in nasal washings in MCS patients and control subjects after controlled and blinded low-level chemical exposures. Biopsies of nasal mucosa of MCS patients and control subjects after chemical exposure might be done to investigate the presence of inflammation. MCS patients should be compared with normal persons and with those with allergic rhinitis.

Future research should involve controlled and objective measurement of the possible neurophysiologic effects of odor or respiratory tract irritation from low levels of volatile organic compounds and other respiratory irritants, perhaps using electrophysiologic or radiologic tools to measure acute or chronic alterations in central nervous system function. Research is also necessary to establish the diagnostic efficacy of such tools as brain electrical activity mapping, single photon emission computed tomography or positron emission tomography scans in measuring changes in central nervous system function in MCS patients. At this time these tools (and other yet-to-be-discovered tests of neurologic dysfunction) should be performed only by appropriately trained health professionals in a research setting using proper methodology and controls for investigation.

Further research is *not* needed to determine whether patients with MCS have an illness characterized by a high prevalence of preexisting and coexisting psychiatric disorders because almost all the studies addressing this problem show that they do.[14, 51, 52, 54, 55, 58]

An epidemiologic, community-based study might further define the sequencing of the development of psychiatric disorders and the onset of MCS. Prospective studies of chemically exposed groups could address whether psychiatric illness is a direct consequence of the syndrome or etiologic by making one more vulnerable to the development of MCS from the psychophysiologic effects of various chemical exposures and/or the adoption of illness belief systems.

One technique that might be used in assessing the similarity of MCS to major depression would be to examine which depression criteria items are endorsed to determine whether the pattern of symptoms in MCS patients differs from those with other forms of major depression. Another technique that may be used to assess the prevalence of psychiatric illness is not to count MCS symptoms toward a psychiatric diagnosis.

Controlled clinical research is needed to determine to what extent various psychiatric, behavioral, and other treatments are effective in different categories of patients with MCS. Clarification of mechanisms of etiology of this syndrome will also aid efforts for prevention.

Further clarification of etiologic mechanisms in MCS is also necessary to determine whether avoidance of environmental exposures thought to precipitate symptoms is to be recommended for MCS patients. The avoidance issue is a major dilemma. Human exposure to toxic levels of any chemical should be avoided, with the use of engineering controls, personal protective equipment, work practices, and, in some cases, job modification or removal. To those who believe that MCS is primarily due to toxic mechanisms such as immunologic injury or neurotoxicity, these forms of avoidance would seem appropriate for very low exposure levels, and treating symptoms, rather than the root cause of MCS, might be harmful. However, there is no convincing evidence that exposure to very low levels of chemical substances exacerbates any underlying disease process or produces pathologic damage in patients with MCS, and there are no data showing that long-term withdrawal from exposure produces an improvement in symptoms. Because major lifestyle modifications frequently lead to substantial and deleterious consequences such as loss of work and social support, the burden of proof rests with the proponents of avoidance that it is effective in reducing symptoms and necessary to prevent toxic injury. It is also acknowledged that this burden of proof would be made easier to bear if major governmental agencies were putting resources into studying MCS.

MCS is rapidly becoming a politically defined illness in the vacuum created by lack of data. Some legislators, administrators of government bodies, and several in the legal profession believe or fear that the current controversy surrounding MCS is similar to that which existed several decades ago regarding asbestos-related lung disease and that medical science simply has not yet found a way to link environmental chemical exposure causally with the illness or to measure the impairment and disability of patients given an MCS diagnosis. Physicians who question or are agnostic about its relationship to workplace or environmental exposure have been targeted by hostile attack from MCS support groups or others with an economic stake in the outcome of the debate: in some cases even being removed from government jobs for the expression of their views (*Seattle Times*. July 17, 1993:A1–A5). In the future, MCS may increasingly impact the country's total burden of chronic disability, much as low back pain and cumulative trauma disorders of the upper extremities do now. It would thus be appropriate to obtain the data necessary to define this condition and its relationship to environmental chemical exposure medically, *before medical science becomes irrelevant to*

the diagnosis, treatment, and social policy decisions relating to MCS.

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The Liquid Silver Lining

As disastrous as a flood is to those in its path, it is nonetheless part of a natural cycle of renewal just as forest fires are. The river channels grow so wide and the currents so strong they lift topsoil, carry nutrients downstream and deposit them in new soil. Iowa's loss may be Missouri's gain, but then Iowa may get its own refill from Minnesota. The heavy rains that precede the flooding can also cleanse the river waters and make a better pool for fish to spawn.

From "The Mississippi Reclaims Its True Domain," by Isabel Wilkerson in *The New York Times*, July 18, 1993, Section 4, pp 1–3