Multiple Chemical Sensitivity: A Primer for Pulmonologists

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Multiple chemical sensitivity is a commonly used diagnostic term for a group of symptoms without apparent organic basis. The symptoms are characteristic of dysfunction in multiple organ systems, wax and wane according to exposure to low levels of chemical agents in the patient's environment, and sometimes begin after a distinct environmental change or insult such as an industrial accident or remodeling. Although traditional medical organizations have not agreed on a definition for this syndrome, it is being increasingly recognized and makes up an increasing percentage of the caseload at occupational/environmental medicine clinics. The prominence of pulmonary complaints and the specific overlaps with asthma symptomatology make it a challenge for the practicing pulmonologist. Recognition of pulmonary aspects of psychiatric syndromes such as hyperventilation, anxiety disorders, and posttraumatic stress disorders is critical to optimum management and therapy. Although there is often dispute about whether the symptoms have a functional or organic basis, an informed approach to evaluation, diagnosis, and management and a careful assessment of impairment, disability, and work relatedness are necessary. Careful exclusion of organic causes, both toxicologic and nontoxicologic, is critical, followed by a judicious approach to coping with what at the end of practical evaluation seems to be mostly functional symptoms. Medical care is often best integrated from a psychosocial perspective.

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CASE EXAMPLE

A 42-year-old color-paint technical specialist was referred for evaluation by his employer. He began working in 1977 for a large manufacturer of automotive specialty paints as a technical specialist in a color laboratory for development of new paints. In 1988, he was assigned to work as a liaison specialist at the assembly plant of a large truck manufacturer where he had supervisory and advisory responsibilities for automotive painting.

He was frequently exposed to sprayed-on paints and solvents and regularly wore a negative-pressure charcoal respirator and a protective garment; paint areas were believed to be well ventilated. In August 1990, a new enamel reducer consisting of acetone, methyl isobutyl ketone, toluene, isopropyl alcohol, and naphtha was introduced. A pruritic rash developed, diagnosed as contact urticaria by a dermatologist and was associated with an immediate patch-test skin reactivity to this solvent, as well as to two other agents, a lacquer thinner consisting of toluene, glycol ether, ethyl isobutyl ketone, acetone, and 2-ethoxy ethanol and a urethane activator consisting of polyisocyanate resin, butyl acetate, and aromatic hydrocarbon resin. On May 1, 1991, an accident occurred wherein the lacquer thinner spilled onto the patient, soaking him and possibly resulting in loss of consciousness. He was taken to a local hospital, but not admitted, and the treatment he received is not known. One month later he had the onset of acute shortness of breath and chest

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tightness upon walking into a paint-spray booth and subsequently had similar episodes in the same setting. In March 1992, he was evaluated by an internist who found a normal examination, normal electrocardiogram, and normal chest roentgenogram. Spirometry results were as follows: forced vital capacity (FVC) = 6.13 liters (131%), forced expiratory volume in 1 second (FEV_1) = 4.65 liters (126%), and FEV_1/FVC = 76%. Based on the patient's history, a diagnosis of work-related bronchospasm was made, and his removal from paint exposure was recommended. On April 30, 1992, a company physician reviewed the case and concurred with the recommendation for the patient's removal from paint-booth exposure, which resulted in the patient's transfer to a facility in another state where he worked in a warehouse stocking and retrieving requested paint-related materials. He still had inhalation exposure to paint products as a result of spills. Dermatologic symptoms diminished while respiratory complaints increased.

A pulmonary evaluation from April to July 1993 resulted in a diagnosis of "hypersensitive airway syndrome, status postchemical inhalation." Treatment was initiated with albuterol, beclomethasone dipropionate, and theophylline extended-release capsules, without substantial improvement, and these medications were discontinued after a period of several months. An allergy evaluation in May 1993 noted symptoms of episodic shortness of breath, dizziness, and disorientation since 1990, improvement on weekends, and complete remission on vacation. Physical examination was normal; no tests were performed; and no diagnosis was given beyond the clarification of work-related symptoms "likely related to isocyanates and other chemicals."

In June 1993, in an attempt to reduce his paint exposure, he was transferred to a third location in eastern Pennsylvania where he performed only office work, although a warehouse was adjacent, separated by a door, where paints were mixed and sometimes sprayed. Odors from the warehouse, as well as perfumes on coworkers, gasoline, fabric softeners, cleaning products, incense, and sweeping compounds, were associated with headache, nausea, upper airway irritation, itching, and burning without shortness of breath and without relief from inhaled bronchodilators. He also found he could not tolerate shopping malls because of frequent triggers of his symptoms by other customers' cosmetics or from stores with strong odors. Symptoms at home were reported to be minimal if cleaning products and cosmetics were avoided.

At the time of our evaluation in fall 1995, he denied ever having been diagnosed with asthma or other pulmonary condition, and although he admitted to episodic shortness of breath, he denied cough, wheezing, chest pain, nasal congestion or rhinorrhea, rheumatologic or thyroid disease, seasonal allergies, or excessive use of alcohol. He also denied depression, unusual anxiety, problems with memory or concentration, and fatigue. Although his reactions to odors produced intense discomfort, they were not associated with feelings of impending doom. He had previously received professional counseling for 6 months in 1991 to 1992 at the time of a divorce. Physical examination was unrevealing, including a normal nasal, pharyngeal, and chest examination. Spirometry results were as follows: FVC = 5.53 liters (128%), FEV_1 = 3.93 liters (110%), FEV_1/FVC = 71%, and forced expiratory flow, mid-expiratory phase = 2.07 liters/second (70%). After two puffs of isoetharine, FEV_1 increased 1%, and FEV_1/FVC also increased 1%. Immunoglobulin E level was 97 ng/mL (range: 0–180).

Symptoms compatible with multiple chemical sensitivity (MCS) syndrome were verified. Asthma and nasal inflammatory or allergic conditions were not believed to be present. Panic/anxiety disorders were not judged to be clinically likely, and this was verified with the use of the Structured Clinical Interview for DSM-III-R (1) (a structured psychiatric interview), which also excluded other axis I psychiatric disorders. The patient was counseled about the nature of chemical sensitivity, and detailed interactions were undertaken with the company, the workers' compensation carrier, and the disability insurance carrier in an attempt to achieve a satisfactory employment situation. No treatment was attempted because the patient resided more than 100 miles from the medical center, although psychotherapy aimed at enhancing the ability to cope with such troubling symptoms was recommended.

This case illustrates both characteristic and uncharacteristic aspects of MCS. Characteristic is the triggered symptoms without a documented underlying disorder, despite years of (unsuccessful) management as a work-related asthmatic. Also characteristic is moving from job situation to job situation without finding comfort, and, in fact, progressively developing more and more restrictions outside the workplace. Somewhat uncharacteristic is the prominence of respiratory symptoms without many cognitive or psychiatric symptoms. He may well have been an excellent candidate for behavioral therapy because he seemed to be well motivated and had kept his job. The insurer, however, was unwilling to support further therapy, and the distance from the medical center precluded continued follow-up. After 6 months of short-term disability at employer expense and a 4-month period where workers' compensation benefits were received but no treatment given, the patient accepted work as a produce clerk in a grocery store. Symptoms persist with exposure to some cleaners and cosmetic products, but these do not prevent his seeking increased hours to maintain a reasonable standard of living at this reduced-wage job.

INTRODUCTION AND DEFINITIONS

There is no widely accepted definition of MCS because there is very little agreement on what the symptoms represent. No definition has yet been endorsed for clinical use by a body of physicians. Both the American Medical Association and the American College of Physicians have considered the general topic and found insufficient scientific rigor to allow recognition of a specific disease entity or to suggest a definition (2,3). Nevertheless, there is a group(s) of patients who present in a way that leads pulmonologists and other clinicians to consider this topic, and, in fact, it is clinically important and useful to recognize distinctions from and overlaps with other diagnostic categories. Recognition, evaluation, and treatment can be done from within a perspective of traditional allopathic, scientifically based practice. We will

focus on those aspects of the presentation and workup of such patients that overlap most closely with and present differential diagnostic dilemmas with respect to common pulmonary conditions, particularly asthma and some of its variants including upper respiratory disorders.

Recognition of MCS is most useful to distinguish persons with medically unexplained symptoms (e.g., fatigue, headache, lack of concentration, and respiratory symptoms) when these symptoms are attributed to and triggered by environmental exposures, because there is no other specific diagnostic label to describe such individuals. Many advocates of the concept of chemical sensitivity, such as the group of "environmental physicians" formerly called "clinical ecologists," espouse a broader definition, which essentially includes all diseases, both those limited to symptoms as above and those defined by tissue pathology, that are judged to be caused or aggravated by chemical exposure. This definition includes cases of vasculitis or asthma whose pathogenesis or course may be attributed to chemicals (4). This review will not take such a broad approach, because it seems that conditions with well-established taxonomies or objective measures lend themselves directly to other investigations, for example, epidemiology and toxicology, which are currently used to address questions of causation. Rather, this review will focus on MCS as a syndrome of unexplained symptoms attributed to chemical exposure. It is important to separate "causes" of this clinical picture from a simple question of whether individuals exist who have triggering of otherwise "unexplained symptoms." Cullen's (5) 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 as stated, is intended to allow physicians to distinguish MCS from other collections of similar, commonly experienced symptoms. It 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 serves to exclude patients with long-standing health problems who later attribute certain symptoms to chemical exposure, although it does not help place individuals who experience a vague or gradual onset of their chemical sensitivity symptoms. It does not necessarily follow in all cases that the "event" was a necessary and sufficient cause of the MCS.
2. Symptoms involve more than one organ system and recur and abate in response to *predictable* environmental stimuli. This provides the salient feature of multiple symptoms and multiple chemicals.
3. Symptoms are elicited by exposures to chemicals that are *demonstrable* but very low. The exposures eliciting symptoms may be substantially below the typical 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 (clinical) test of organ system function can explain the symptoms, and there is not objective evidence of explanatory organ system damage or dysfunction.

An alternative and clinically useful definition proposed by Simon and colleagues in 1990 (6) took an operational approach and stated that anyone who endorsed at least three of the following four items could be considered to have MCS:

1. I have changed my diet because of chemical sensitivity.
2. I have changed by home furnishings or furniture because of chemical sensitivity.
3. I have changed the clothes I wear because of chemical sensitivity.
4. I have changed the stores I shop in because of chemical sensitivity.

In our experience there is a high level of agreement between individuals who, on clinical evaluation, meet the Cullen criteria and those who endorse three or four of these items (7). A major practical limitation of all available definitions of MCS 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, because there are no clinical challenge protocols established to be valid and reliable.

CLASSIFICATION AND NATURAL HISTORY

For this condition with no clear definition, there is no established system for classification that can be used to identify subgroups with differing prognoses. However, the available literature suggests useful guideposts for individual patients, especially in terms of comorbidity and severity. A key consideration is whether a diagnosable psychiatric condition exists. Higher rates of diagnosable anxiety, depression, somatization, phobias, and perhaps personality disorder exist when various studies have compared MCS subjects with control subjects (8). Although rates are not necessarily higher than for other groups of patients with unexplained symptoms, they do reach about 50%, sometimes 70%, far higher than in the general population. This is an important point for classification, because these conditions may be amenable to improvement with established psychiatric treatments. There is also a high correlation between the presence of psychiatric comorbidity and whether the MCS is reported to have a clear, defining onset, as in the first Cullen criterion (lower psychiatric comorbidity), or whether it developed gradually without a sudden overexposure incident (higher psychiatric comorbidity) (7). Many clinicians believe that individuals who have a sudden onset after one or a series of fairly high-level exposures, clearly suggesting the presence of anxiety disorders such as posttraumatic stress disorder (PTSD), atypical PTSD, or panic attacks, should be aggressively identified and receive treatment for anxiety disorder.

Severity can be scaled in various ways, but no scale has been validated. Perhaps most important is whether the individual is still working. This is one milestone in assessing the extent of "avoidance" or withdrawal from triggering exposures. Also key is whether the individual has embraced alternative therapies and lifestyles. Once this has occurred, prognosis seems more

problematic because most accepted therapeutic approaches include psychiatric and behavioral treatments that are not well received by many alternative practitioners and patients who rely on them.

Respiratory symptoms are common but not usually predominant in MCS. Frequencies of lower and upper respiratory symptoms are shown in Table 1 along with comparison rates using the same self-administered questionnaire in research subjects with chronic fatigue syndrome (CFS) and normal control subjects. In one series of 35 MCS patients from an occupational health clinic, the nine most frequently reported symptoms did not include any attributable to the upper or lower respiratory tract (9), whereas in our population of MCS research subjects recruited from medical referrals, only one, shortness of breath, was in the top 10, with fatigue, weakness, and central nervous system (CNS) symptoms more common.

Patients will frequently attribute changes in severity of symptoms to control of exposure or lack of exposure, but this has not been studied. MCS is not known to be progressive in terms of measurable physical dysfunction or development of complications such as infection, dementia, and death. Despite this "good news" complete remissions are not often described. Symptomatic reactions to chemicals tend to persist, although some individuals learn to cope with such symptoms and achieve relatively normal levels of function and remain employed.

EPIDEMIOLOGY

No population-based studies of a prevalence or incidence of MCS according to the definitions used herein have been published. Kipen and colleagues (10) in New Jersey have reported that individuals diagnosed with MCS by the Cullen criteria endorse more substances as giving them symptoms than do comparison groups of clinic patients, although there was wide variation among control subjects, with medical patients endorsing significantly more substances than healthy control subjects. Asthmatics, who were stratified separately, reported significantly higher mean numbers of substances than any other group except the MCS group, and a number of the items that were reported as common triggers of symptoms among asthmatics were also common in MCS subjects (e.g., perfumes and insecticides). This is consistent with a limited but plausible body of literature that documents bronchoconstriction in response to perfume constituents, although effects of odor versus irritation are not well discriminated in this existing literature (11). Thus, symptoms in response to odors ("sensitivity") are widespread and more common in asthmatics. However, available data are inadequate to document the prevalence of the entire disabling behavioral syndrome of MCS nor to precisely define its relationship to respiratory diseases.

Two recent studies have documented the presence of chemical sensitivity symptoms in patients with fibromyalgia and CFS, as well as the prevalence of CFS symptoms in those recruited as MCS subjects (7,12). These overlaps may provide important clues to a clear understanding of the scope of chemical sensitivity symptoms and their pathogenesis.

A few groups of chemicals have been implicated as initiating agents in many of the reported cases, particularly respiratory irritants, odiferous organic solvents, and pesticides (frequently applied with solvent vehicles) (13). It is important to note, however, that these agents are in widespread use, and associations have not been formally studied. Many cases also arise out of sick-building syndrome outbreaks, where the MCS cases seem to evolve from typical sick-building syndrome cases. In general, the epidemiology of SBS is that a substantial percentage of individuals who share a common environment develop symptoms that remit when away from the building and that are ameliorated by environmental remediation. Individuals with MCS usually develop persistent symptoms that occur in other settings and generalize to other, usually odiferous, triggers.

ETIOLOGIC THEORIES

MCS, by definition, occurs in a setting of concern about or perception of chemical exposure. There are a multitude of explanatory mechanisms, most based on fairly limited observation. For simplification, they may be grouped into four categories: pathologic and toxicologic, psychophysiologic, psychiatric, and belief systems. In many individuals, more than one of these will seem to be operative, and, in fact, the idea of complete distinctions between psychophysiologic, pathologic, and psychiatric may, at times, be artificial.

The relationship between MCS and environmental chemical exposures has generally not been shown to meet criteria for causality in terms of epidemiologic data, dose response, and established mechanisms (14), but we will consider the evidence for proposed mechanisms that relate to or involve the respiratory system.

Pathologic and Toxicologic Theories

MCS patients typically report heightened odor sensitivity. Researchers initially conceptualized that this could be due to a reduced odor-detection threshold. No significant differences between MCS and control subjects in

TABLE 1. *Respiratory symptoms in MCS, CFS, and control patients (%).**

Respiratory System	MCS (N = 22)	CFS (N = 17)	Control Patients (N = 16)
Dry cough	68	41	39
Cough with phlegm	50	47	44
Wheezing	45	12	6
Shortness of breath	77	65	6
Pain with breathing	50	29	0
Persistent nasal congestion	50	59	33
Persistent runny nose	27	29	33

* Unpublished data collected for subjects with multiple chemical sensitivity (MCS), chronic fatigue syndrome (CFS), and control patients as described in Fiedler et al. A controlled comparison of multiple chemical sensitivity and chronic fatigue syndrome. Psychosom Med 1996;58:38–49.

the ability to detect phenylethyl alcohol (a rose scent), methyl ethyl ketone, or pyridine, a noxious trigeminal stimulant, were found (8,15). However, at suprathreshold concentrations of phenylethyl alcohol, but not pyridine, MCS subjects reported significantly more and more intense symptoms than control subjects, confirming the phenomenon of increased responsiveness in MCS patients to a generally pleasant stimulus, once it was perceptible (8).

MCS subjects have shown increased nasal resistance both before and after testing with odorants, whereas control subjects showed increased resistance only after testing (15). Abnormal rhinolaryngoscopic findings including edema, excessive mucous, and cobblestoning of the posterior pharynx have been reported (16). MCS has also been hypothesized to represent an amplification of the nonspecific immune response of the nasal mucosa to low-level irritants mediated by altered function of the nonadrenergic, noncholinergic (C fiber) nervous system in the nasal epithelium (17,18).

In summary, these findings suggest that MCS patients do not detect odors at lower thresholds, but they may respond more markedly once odors are detected. The relationship of this finding to nasal pathology and increased nasal resistance is unexplored, and the pathologic findings require confirmation with controlled studies.

Psychophysiologic and Psychiatric Theories

Some investigators have proposed that a behaviorally conditioned response to odor could explain some MCS cases (19,20). Initially, a strong-smelling chemical irritant causes a direct and nonconditioned physical or psychophysiologic response. Such a severe chemical exposure may act as an "unconditioned stimulus," producing one trial learning of a conditioned neuropsychologic response, so that subsequently the same odor at a lower nonirritating concentration causes a conditioned response of the same symptoms. Some individuals actually have been shown to be predisposed to psychophysiologic responsiveness in certain organ systems, such as the lung in an asthmatic who develops bronchoconstriction in response to many different psychologic stimuli (21). The prevalence of such a phenomenon in patients who otherwise meet criteria for MCS has not been studied, nor is it clear how this mechanism applies to MCS, wherein the stimulus generalization seems so wide and symptoms occur in many organ systems.

Some specific physiologic indicators of disease can be triggered by suggestion. A number of studies have provided evidence that clinically significant bronchoconstriction can occur in 5% to 25% of asthmatics when individuals simply believe that exposure to an asthma trigger has occurred when, in fact, it has not (21). Nonasthmatics do not display such a clinically significant response, although a brief, small, but statistically significant, response does occur (22).

Many physical and emotional stressors produce hyperventilation, as do a variety of pulmonary, renal, cardiovascular, and other disease states. Symptoms of hyperventilation are extraordinarily varied and can include some common symptoms of MCS: headache, dyspnea, palpitations, tremor, panic, pain, and even seizure activity (23). There is as yet no data on the association of hyperventilation with MCS symptoms, but this is one mechanism for production of symptoms in multiple systems.

There are intriguing case reports in which organic solvents (19,24,25) have been associated with panic attacks. The importance of panic attacks in otherwise unexplained symptoms has been recently reviewed (26). The useful 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 has been proposed (27). The suggestion is made that odor can produce annoyance and autonomic arousal, which then may be amplified in a person with predisposing cognitive, personality, or biologic susceptibility. Other theories of causation of MCS propose more complex biologic mechanisms for the conditioning model described above, relying on interaction between the olfactory, nervous, and endocrine systems to explain odor-triggered symptoms (14,28).

It has been proposed that MCS is a misdiagnosis and chemical exposure is not the cause of the symptoms, which are actually due to primary psychiatric disease. A handful of controlled studies demonstrates the importance of psychologic manifestations, if not necessarily causes, in MCS patients, but also shows the absence of a diagnosable axis I (mood, anxiety, substance, somatoform, sleep, eating, adjustment, or psychotic, but *not* personality) disorder in 30% to 50% of subjects (8,14).

Belief Systems

Many scientists, physicians, and others have postulated that in many ways MCS is a belief system (14) promoted by clinical ecologists and those sympathetic to their views and followed by medically unsophisticated persons. 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 (29,30).

The available evidence shows that patients diagnosed with MCS are very heterogeneous and that more than one causal mechanism may be operative in some cases. It is an intriguing possibility 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 occurs as a result of one or more of the mechanisms proposed above.

DIAGNOSTIC EVALUATION

Even more so than with typical exposure-related evaluations, the evaluation of a patient presenting with MCS may take several hours. In clinical practice, there may be some confusion between acute and chronic occupational or environmental illnesses associated with objective signs of disease and MCS, although some patients may have both. As in the case example presented here, it is not infrequent for individuals who eventually qualify for a diagnosis of MCS to have been previously treated as asthmatics, with the eventual recognition by patient and physician that airway disease is not predominant.

From a practical point of view, differential diagnostic problems occur in two settings. The first, as demonstrated with the example, is when early in the course of the MCS, it is difficult to distinguish it from the preceding occu-

pational problem. Care must be taken to distinguish MCS reactions that lack a prominent bronchoconstrictive component from those characterized by bronchoconstriction. Once a situation of improper exposure has been corrected, for instance, after the solvent spill described, the asthmatic who has also developed MCS may continue to react symptomatically in the office, perhaps without significant bronchoconstriction. Later in the course of MCS, diagnosis may be complicated by the development of more severe anxiety and depression as a consequence of having a chronic condition, although this is unstudied. Subsequent exaggeration of psychiatric symptomatology may lead such symptoms to overshadow chemically triggered symptoms. Notwithstanding the possible psychologic origins of MCS, validation of the MCS symptomatology may allow development of treatment strategies acceptable to the patient.

A pitfall to avoid is making an inappropriate diagnosis of MCS for patients with well-defined toxic or allergic disease or irritant injury, such as asthma, lead intoxication, or allergic alveolitis, and thus possibly failing to provide appropriate treatment. There also may be some comorbidity with other specific occupational conditions (e.g., solvent intoxication, allergic alveolitis) and MCS, as when symptoms of upper respiratory irritation fail to resolve with removal from exposure or when symptoms spread beyond the traditionally affected organ system, as when mild asthmatics become more disabled by cognitive rather than respiratory symptoms.

Medical History

The keys to diagnosis and clinical management of the individual presenting with suspected or previously diagnosed MCS include a detailed exposure history and a comprehensive medical and psychosocial evaluation of the patient. The baseline medical and psychiatric status of the patient before development of the presenting symptoms needs to be established. Current and previous illnesses, diagnostic evaluations and treatments, and the possibility of a long history of unexplained physical symptoms or excessive medical care should be sought. It is not unheard of for patients presenting with MCS to have long histories of similar symptoms, lacking chemical attribution (31). This certainly suggests that the disorder is not acquired in these cases.

The exposure history is key for an understanding of potential causal factors. In addition to establishing the history of symptoms triggered by exposures that are tolerated by most others, it is important to flesh out the circumstances of the initiating exposure. Exclusion of traditional toxic conditions and also consideration of the toxin-induced psychiatric syndromes such as PTSD and toxin-induced panic attacks must be addressed. It must be determined if, in fact, there was a substantially unusual exposure, such as an accident, the evacuation of a building, or other circumstance, raising the possibility of both chemical damage and psychologic trauma. The physician needs to estimate concentration and duration of exposures to determine the probability that the symptoms were or are due to a known toxic or irritant effect.

Physical Examination

A physical examination is performed largely to identify other medical conditions. Care should be taken to examine and carefully record findings that relate to reported symptoms, for example, skin rash, nasal mucosal irritation, nasal deformities, and mental status. Trial removal from the environmental chemical exposure of concern for a short time may have diagnostic value; short-term removal may also have palliative value while arranging interventions that are more suitable for long-term case management.

Diagnostic Testing

The evaluating and treating physicians must be wary about excessive ordering as well as the misinterpretation of diagnostic tests. Excessive testing, as often ordered by those who are not sophisticated in the evaluation of chemical exposure questions, may reinforce a detrimental pattern of illness behavior, and most management strategies for other unexplained symptom syndromes such as somatization include judicious use of a primary care physician as a gatekeeper to reduce unwarranted testing and its medical and psychologic complications. At this time, there is no test that has been established for the diagnosis of MCS per se. Diagnostic testing in patients with symptoms of MCS should be used primarily to identify the presence of other environmental or nonenvironmental illness in the differential.

In the overwhelming majority of cases, results of diagnostic tests do not explain the multiorgan symptoms of MCS. For example, if airway reactivity is documented, this does not readily explain CNS, gastrointestinal, visual, or other organ system complaints. In addition, subtle variations in physiologic testing may be hard to distinguish from normal variability in a heterogeneous population, and caution is necessary so as not to overinterpret results as an explanation for the patient's symptoms. Interestingly, some percentage of patients who present with respiratory symptoms resembling MCS may have more specific functional abnormalities, such as vocal cord dysfunction or laryngeal dyskinesis, manifest by an abnormal flow volume loop, which can be treated through specific behavioral approaches (32). Abnormalities that are difficult to explain are intriguing and challenging, but are not necessarily, or even likely, an indicator of MCS, which to date, has no characteristic laboratory or test findings.

Many tests that have been asserted to characterize MCS patients fall into the general realm of neurophysiology or neuroimaging. No test of CNS effects has been validated through clinical research, with proper control subjects to guide use and interpretation, to confirm the presence of MCS (33). Bona fide abnormalities on such investigations do more to raise the question of another condition in the differential diagnosis, such as solvent encephalopathy or a neurodegenerative disorder.

Because of the widespread clinical use and assertion that MCS could be characterized by abnormalities of immune system activation, specific antibodies, and lymphocyte subtypes, these immunologic tests have been studied in a limited number of controlled trials. No form of immunologic testing has been shown to be diagnostic of either exposure to specific chemicals or illness in patients with MCS (8).

Neuropsychologic testing is dependent on patient cooperation and might be useful to rule out other conditions in the differential diagnosis, but this cur-

rently does not reveal consistent or specific findings in MCS patients that may be used for diagnosis (7,34). Definitive research using appropriate control subjects on controlled challenge procedures is necessary before they can be recommended as useful tools for diagnosis. (8,35,36). The clinical use of environmental challenge units for diagnosing MCS remains controversial. The problems with this approach are that we usually do not know the actual level of environmental exposure causing symptoms, testing of substances having distinct odors or irritant properties cannot readily be done in a blinded fashion, and proper control subjects and objective measures of response that are relevant to the patient's symptoms are unavailable.

Psychiatric Evaluation

Psychiatric evaluation of the patient given a diagnosis of MCS may be appropriate for some persons, given the high prevalence of coexisting or preexisting psychiatric disorders in these patients. Unfortunately, many patients given a diagnosis of MCS resist the idea that psychologic factors may play any etiologic role at all in their distress; however, this should not necessarily be interpreted that the patient has a primary psychiatric illness. The stigma placed on psychiatric disorder in our society probably plays a major role in the tendency to somatize. The adamant rejection of psychologic factors in symptom formation and expression by MCS patients is a challenge for the physician who must establish a workable strategy for approaching this issue that is both sensitive to the patient's feelings and still effective in exploring possible emotional contributors to the syndrome. If the physician merely queries the patient as to the effect the illness has had on lifestyle and mood, many patients report and discuss symptoms of depression and anxiety freely. This may allow an opening to refer for either diagnosis or treatment.

CLINICAL MANAGEMENT

Very little is known about the proper treatment of MCS. No therapy has been subjected to controlled clinical trials to confirm short- or long-term efficacy with these patients. Approaches to treatment have paralleled etiologic theories and have recently been reviewed (37).

Clinical Ecology Approaches

Clinical ecologists and other nontraditional practitioners who believe that MCS is due to immune dysfunction caused by elevated body burdens of exogenous chemicals have championed the importance of avoidance of chemical exposure. Avoidance has been augmented by strategies to enhance immunity with dietary supplements and antioxidants. Another approach has been to eliminate toxins from the body with chelation techniques or promotion of excretion of lipid-soluble toxins by use of sauna therapy, the use of which is vitiated by the absence of data to support a role for chemical overload as a cause of MCS (14,37).

Medical Approaches

To the extent that atopic allergy or nasal pathology is identified in MCS patients, therapy for symptom control should be maximized. This is rarely a cure, but can provide some relief of symptoms.

Psychologic Approaches

Practitioners who have a more psychologic view of MCS have tried to apply pharmacologic and behavioral techniques developed for management of the underlying psychopathology. Group therapies have been tried, but in our experience these have substantial risk of reinforcing disabling avoidance because of the sharing of counterproductive (mis)information among participants.

Searching for a specific cause in patients who meet MCS criteria should be minimized, as the yield is negligible, especially after a long evaluative course, and may interfere with appropriate focus on symptom management strategies by reinforcing a belief in organic pathology. The state of existing knowledge and uncertainty about MCS should be explicitly explained so that the patient can begin to accept that the cause is essentially unknown. A supportive and nonjudgmental approach to the patient may open the way for reassurance about the importance of psychologic factors as modifiers of underlying symptoms. This can be explained, encouraging patients to accept psychologic issues and mechanisms as potentially modifiable factors in their discomfort. Reassurance should be given that MCS is not known to lead to progressive organ failure or death, and the patient should also be told that a complete "cure" is unlikely at the present time.

Many patients will admit that their symptoms are worse when they are under emotional stress and that they can benefit from some stress management advice or therapy, such as progressive relaxation training and cognitive coping skills. Hyperventilation should be identified and approached through breathing control, stress management, and education, often available in a behavioral medicine clinic. More severe symptoms of depression or anxiety should be medically managed with psychotropics, notwithstanding the difficulties with side effects discussed below. Poor sleep should be addressed. Enhancing the patient's sense of control over workplace or home stressors, including environmental chemical exposures, is likely to be effective in managing symptoms.

Systematic changes in the organization of work may be needed to reduce organizational stress. Odors and exposure to volatile organic compounds in the workplace and home, which are perceived as irritating or noxious by the symptomatic person, should be reduced and controlled as much as possible. This should be attempted, even if levels of exposure are below government-mandated or -recommended permissible exposure limits; these standards may be inadequate to prevent symptoms in unusually sensitive workers. Although radical avoidance is inimical to enhancement of function at work, the ability to use judicious avoidance for control of regular and severe symptoms may foster the kind of therapeutic relationship on which progress may be built. Balancing the benefits of any avoidance measures with the potential risks of a spiraling pattern of progressively severe environmental restrictions and loss of employment is the ultimate challenge with the MCS patient who is still employed. Consideration of these issues may be enhanced by a clear discussion of the costs and benefits of avoidance.

The fundamental principle of behavioral approaches is symptom desensitization by gradually increasing exposure in an organized program allowing for accommodation and increasing tolerance. Biofeedback may be useful in modifying body sensations. This approach assumes that an important contributing factor to the manifestation of MCS is primarily behavioral without associated objective or progressive physiologic impairment, dysfunction, and disease. Cognitive behavioral therapy for medically unexplained symptoms, not specifically including MCS, has recently been shown to be effective in a randomized clinical trial from The Netherlands (38). Another group identified three MCS patients who met criteria for simple phobia, and were, at least initially, successfully treated by an intensive desensitization program consisting of biofeedback-assisted relaxation training, in vivo exposure to offending chemicals, and cognitive restructuring procedures (39). Patients who, after supportive counseling, continue to deny that stress or psychologic factors might play any role at all in their symptoms, probably cannot be helped by any of the above therapies.

WORK RELATEDNESS

This is obviously a key issue and a very difficult one to address. Despite the absence of objective findings of disease to explain symptoms in patients given a diagnosis of MCS, the syndrome may be severely distressing and functionally disabling, even as patients increasingly avoid universally present chemical exposures. Using the definition and workup that have been suggested, we are left mostly with a consideration of unexplained symptoms and psychologic issues. In those cases where an individual progresses rapidly from a satisfactory level of job performance to an unsatisfactory one, with prolonged or multiple absences, we must address precipitating external factors. Not infrequently, a clear and identifiable inappropriate exposure incident occurs that generates "explained" symptoms such as respiratory irritation or CNS intoxication. When the symptoms subsequently progress to MCS, work relatedness may be reasonably inferred. Diagnoses such as PTSD or odor-induced panic attacks may be an underlying explanation and deserve compensation, as well as directed behavioral and/or pharmacologic intervention. When the precipitating exposure is more prolonged or not identifiably capable of inducing symptoms, the situation is much less clear-cut. Many sick-building episodes fall into this latter group, although again, if there were a clear-cut incident, such as a building evacuation, compensation for the sequelae of that event may be reasonable. If the sequelae are such that the person becomes totally disabled in the absence of organic disease, this is more problematic and needs to be considered carefully. In many workers' compensation systems, factors that aggravate a preexisting condition are compensable, and thus again, even preexisting psychologic (excessive healthcare utilization for unexplained symptoms) or physiologic (e.g., airway hyperactivity) vulnerabilities may not preclude a consideration of the role of later factors that precipitate a decompensation.

REFERENCES

1. Spitzer RL, Williams JB, Gibbon M, First MB. Structured clinical interview for DSM-III-R (SCID) user's guide. Washington, DC: American Psychiatric Press, 1990.
2. Council on Scientific Affairs, American Medical Association. Clinical ecology. JAMA 1992; 268:3465–7.
3. American College of Physicians. American College of Physicians position statement: clinical ecology. Ann Intern Med 1989;111:168–78.
4. Rea WJ. Chemical sensitivity, vol. 1. Boca Raton, FL: Lewis Publishers, 1992.
5. Cullen MR. The worker with multiple chemical sensitivities: an overview. In: Cullen M, editor. Occupational medicine: state of the art reviews. Philadelphia: Hanley & Belfus, 1987: 655–61.
6. Simon GE, Katon WJ, Sparks PJ. Allergic to life: psychological factors in environmental illness. Am J Psychiatry 1990;147:901–6.
7. Fiedler N, Kipen HM, DeLuca J, Kelly-McNeil K, Natelson B. A controlled comparison of multiple chemical sensitivity and chronic fatigue syndrome. Psychosom Med 1996;58:38–49.
8. Fiedler N, Kipen HM. Chemical sensitivity: the scientific literature. Environ Health Perspect. In press.
9. Lax MB, Henneberger PK. Patients with multiple chemical sensitivities in an occupational health clinic: presentation and follow-up. Arch Environ Health 1995;50:425–31.
10. Kipen HM, Hallman W, Kelly-McNeil, Fiedler N. Measuring chemical sensitivity prevalence: a questionnaire for population studies. Am J Public Health 1995;85:574–7.
11. Shim C, Williams M. Effect of odors in asthma. Am J Med 1986;80:18–22.
12. Buchwald D, Garrity D. Comparison of patients with chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivities. Arch Intern Med 1994;154:2049–53.
13. Miller CS, Mitzel HC. Chemical sensitivity attributed to pesticide exposure versus remodeling. Arch Environ Health 1995;50:119–29.
14. Sparks PJ, Daniell W, Black DW, et al. Multiple chemical sensitivity syndrome: a clinical perspective. I. Case definition, theories of pathogenesis, and research needs. J Occup Med 1994;36:718–30.
15. Doty R, Deems DA, Frye RE, Pelberg R, Shapiro A. Olfactory sensitivity, nasal resistance and autonomic function in patients with multiple chemical sensitivities. Arch Otolaryngol Head Neck Surg 1988;114:1422–7.
16. Meggs WJ, Cleveland CH. Rhinolaryngoscopic examinations of patients with the multiple chemical sensitivity syndrome. Arch Environ Health 1993;48:14–8.
17. Bascom R. Multiple chemical sensitivity: a respiratory disorder? Toxicol Ind Health 1992;8: 221–8.
18. Meggs WJ. Neurogenic inflammation and sensitivity to environmental chemicals. Environ Health Perspect 1993;101:234–8.
19. Bolla-Wilson K, Wilson RJ, Bleecker M. Conditioning of physical symptoms after neurotoxic exposure. J Occup Med 1988;30:684–6.
20. Lehrer P. Psychophysiological hypotheses regarding multiple chemical sensitivity syndrome. Environ Health Perspect. In press.
21. Isenberg SA, Lehrer PM, Hochron S. The effects of suggestion and emotional arousal on pulmonary function in asthma: a review. Psychosom Med 1992;54:192–216.
22. Kotses H, Rawson JC, Wigal JK, Creer TL. Respiratory airway changes in response to suggestion in normal individuals. Psychosom Med 1987;49:536–41.
23. Fried R. The hyperventilation syndrome. Baltimore: The Johns Hopkins University Press, 1987.
24. Dager SR, Holland JP, Cowley DS, et al. Panic disorder precipitated by exposure to organic solvents in the workplace. Am J Psychiatry 1987;144:1056–8.
25. Shusterman D, Balmer J, Cone J. Behavioral sensitization to irritants/odorants after acute overexposure. J Occup Med 1988;30:565–7.
26. Smoller JW, Pollack MH, Otto MW, Rosenbaum JF, Kradin RL. Panic anxiety, dyspnea, and respiratory disease. Am J Respir Crit Care Med 1996;154:6–17.
27. Shusterman DJ, Dager SR. Prevention of psychological disability after occupational respiratory exposures. In: Harber P, Balmes JR, editors. Prevention of pulmonary disease. Occupational medicine: state of the art reviews. Philadelphia: Hanley & Belfus, 1987:11–27.
28. Bell IR, Schwartz GE, Baldwin CM, et al. Individual differences in neural sensitization and the role of context in illness from low level environmental chemical exposures. Environ Health Perspect. In press.
29. Cullen MR. Multiple chemical sensitivities: development of public policy in the face of scientific uncertainty. New Solutions. 1991 Fall; 16–24.
30. Spurgeon A, Gompertz D, Harrington JM. Modifiers of non-specific symptoms in occupational and environmental syndromes. Occup Environ Med 1996;53:361–6.

31. Terr AI. Environmental illness: a clinical review of 50 cases. Arch Intern Med 1986;146: 145–9.
32. Nahmias J, Tansey M, Karetzky MS. Asthmatic extrathoracic upper airway obstruction: laryngeal dyskinesis. N J Med 1994;91:616–20.
33. Mayberg H. Critique: SPECT studies of multiple chemical sensitivity. Toxicol Ind Health 1994;10:661–6.
34. Simon G, Daniell W, Stockbridge H, Claypoole K, Rosenstock L. Immunologic, psychological and neuropsychological factors in multiple chemical sensitivity: a controlled study. Ann Intern Med 1993;119:97–103.
35. Staudenmayer H, Selner JC, Buhr MP. Double-blind provocation chamber challenges in 20 patients presenting with "multiple chemical sensitivity." Regul Toxicol Pharmacol 1993;18: 44–53.
36. National Research Council. Addendum to biologic markers in immunotoxicology. Washington, DC: National Research Council, 1992.
37. Sparks PJ, Daniell W, Black DW, et al. Multiple chemical sensitivity syndrome: a clinical perspective. II. Evaluation, diagnostic testing, treatment, and social considerations. J Occup Med 1994;36:731–7.
38. Speckens AEM, van Hemert AM, Spinhoven P, Hawton KE, Bolk JH, Rooijmans HGM. Cognitive behavioural therapy for medically unexplained physical symptoms: a randomised controlled trial. BMJ 1995;311:328–32.
39. Guglielmi RS, Cox DJ, Spyker DA. Behavioral treatment of phobic avoidance in multiple chemical sensitivity. J Behav Ther Exp Psychiatry 1994;3:197–209.