Invited Commentary: Sensitivities to Chemicals—Context and Implications

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The ground-breaking manuscript on chemical sensitivity symptoms by Kreutzer et al. (1) brings some long overdue rigor to the epidemiology of what has come to be called multiple chemical sensitivity (MCS). It also provides an opportunity to highlight work important to public health in an overlooked field, that of medically unexplained somatic symptoms. MCS along with other syndromes associated with unexplained somatic symptoms often receives relatively short scientific shift.

Symptoms (e.g., headache, fatigue, trouble concentrating) account for a high proportion of medical encounters, and a surprising majority are not explained by pathologic medical conditions (2, 3). Rather than simply dismiss these “unexplained symptoms,” over at least the past two decades, practitioners and patients have coalesced these symptoms into syndromes including chronic fatigue syndrome (CFS), fibromyalgia (FM), irritable bowel syndrome (IBS), atypical connective tissue disease after silicone breast implants, chronic hypoglycemia, sick building syndrome (non-specific building related illness), MCS, and, most recently, Gulf War Illness. Some of the names, such as CFS, do not imply etiology or pathophysiology, while others, such as MCS, invoke chemical triggering of symptomatic episodes as well as the often implied chemical initiation of the sensitivity. Investigators have pointed out the substantial overlap between one unexplained symptom classification and another, such that 30–50 percent of individuals with CFS, FM, and MCS qualify (based on self-report of symptoms) for at least one of the other diagnoses (4, 5). All are unexplained because, despite many theories and hypotheses, there is no acceptance by the medical community of a demonstrated pathology or etiology for the symptoms.

Psychiatric explanations and nomenclature have less than a perfect fit for many cases of unexplained somatic symptoms, not withstanding the significant (sometimes over 50 percent for MCS and CFS) comorbidity for anxiety and/or depression (5, 6). The purest psychiatric diagnosis for an unexplained symptom syndrome is somatization disorder. However, many individuals who seem to have the other syndromes do not qualify for somatization disorder based on existing criteria. True, somaticizers seem to represent the far tail of a distribution of the general tendency to develop and/or express somatic complaints with and without underlying pathology. MCS is a disorder which may sample from this far end of the tail of the somatizing distribution, but in which the symptoms are explicitly linked to environmental stimuli reported by the patient. Certainly it is well accepted that the reporting of symptoms can be triggered by an environmental stimulus which does not induce observable organic pathology, as embodied in the psychiatric anxiety diagnosis of post-traumatic stress syndrome. It is unlikely that all individuals are equally susceptible to symptom induction by such stimuli.

An unanswered (and perhaps as yet unasked) question is: are there more unexplained symptoms in the general population than in previous eras, or at least in the population seeking care? In theory, with more sophisticated imaging and diagnostic techniques, one would predict more explained symptoms and fewer unexplained symptoms. Is this the case? While the answer is not known, one cannot sanguinely anticipate this reduction, given that there are many other determinants of symptoms than currently recognizable pathology. This was clearly described by Spurgeon et al. (7), as shown in the model in figure 1. In light of Kreutzer et al.’s finding of a relatively high prevalence of MCS symptoms, it is particularly intriguing to consider this societal question.

Kreutzer et al. (1) provide a mixture of both surprising and expected information on the medically unexplained symptoms that have come to be labeled as MCS. In the expected category are that symptoms

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Abbreviations: BRFS, Behavior Risk Factor Survey; CFS, chronic fatigue syndrome; FM, fibromyalgia; MCS, multiple chemical sensitivity.

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associated with chemical sensitivity are fairly prevalent in the general population, are more severe in asthmatics, and have a variable relation to disability and medical diagnosis. Very surprising are the magnitude of the general prevalence of sensitivity to chemicals (15.9 percent), the frequency of reported physician diagnosis of MCS or environmental illness (63 percent), and, most surprising, the relatively weak role of gender in determining symptoms, and the very weak role of socioeconomic status and race/ethnicity. The use of the BRFS makes these data highly reliable and generalizable, at least within California.

What is lacking of course is any clear understanding of what the symptoms functionally mean to individuals in terms of behavior or disability. It is also true that we remain near ground zero in addressing whether the underlying cause(s) of such symptoms are biologic, and, if so, whether they are pathologic. Some investigators are beginning to uncover potentially relevant biologic differences between persons who suffer from unexplained symptom syndromes and persons who do not. Among examples of this are the finding of elevated Substance P levels in the CSF of persons with clinical fibromyalgia (8). Their “unexplained” symptoms would move from the right side of the model in figure 1 to the left side, or would at least have dual explanations. While all behavior and symptomatology are at some level grounded in brain function (9), there still remain useful and necessary distinctions, at least for treatment if not etiology, between those conditions clinically diagnosed dominantly by behavior, e.g., depression and anxiety, and those diagnosed dominantly by physiology, e.g., seizure disorders and multiple sclerosis.

There are some seeming paradoxes in the data reported by Kreutzer et al. (1). Only 56 percent of subjects with a physician diagnosis “of environmental illness or MCS” reported that they were unusually sensitive or allergic to everyday chemicals such as household cleaning supplies, paints, perfumes, soaps, and garden sprays. Also the fact that one of five asthmatics was told of “environmental illness or MCS” by his/her physician suggests important underlying issues in the survey which need to be explored with patients and physicians in further studies before concluding that all of this 6 percent is prevalent MCS. It has been observed previously (10—12) that there are substantial overlaps between the symptoms and triggers of MCS and those of asthma, if not necessarily in the pathology of the two conditions.

In the survey, the primary question to determine whether a person self-identified as “unusually sensitive” to things actually asked if they were “allergic or unusually sensitive.” Although the list of examples did not include typical immunoglobulin E (IgE) allergens, it did include many things such as perfumes and cleaning supplies which a proportion of allergic asthmatics and other atopics might consider as symptogenic. Of relevance is that Meggs et al. (13) surveyed a random sample of rural North Carolinians by telephone, and, with a 71 percent response rate, found that 35 percent reported sickness after smelling chemical odors (chemical sensitivity), 35 percent reported sickness after “natural things” (allergy), and 16.9 percent reported both kinds of response. The respective roles of the concept of IgE allergy, irritancy, and airway (upper and lower) reactivity in these percentages needs to be apportioned, as MCS is most usefully considered as a proposal to explain things not adequately explained by established concepts such as asthma.

These data are both challenging and reassuring to those in many industries who deny the link of chemical sensitivity symptoms to chemical exposures. While overall percentages of sensitivity are high, specific

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The challenge remains to distinguish between symptoms as reported by Kreutzer et al. and objective indicators of disordered behavior. For example, within the field of environmental and occupational health, during the past 20 years investigators have used sophisticated neurobehavioral tests to quantify symptomatic complaints such as poor memory and concentration when no obvious pathology could be detected (15, 16). Prior to the application of these methods, investigators and clinicians had only symptoms to document the effects of chronic, long-term exposures to such neurotoxicants as pesticides and organic solvents. The exposures reported by MCS patients to produce symptoms, however, appear to be orders of magnitude below those exposures that result in quantifiable deficits in neurobehavioral test performance, leaving us without a mechanism for the claimed effects. Thus, the challenge will be to find methods that test objectively symptoms reported both in the population and among clinical cases. Is this an unusual susceptibility to exposure among a few clinical cases or an unusual response of a few clinical cases to exposure-related symptoms that many in the population experience?

What can be made of this and where do we go from here? We clearly need much more epidemiology to pursue more detailed characterization of sensitive individuals as compared to other population groups, both healthy and those with various disease states. This should include more population-based studies of symptom prevalence with follow-up studies of what symptoms mean to individuals in terms of their interpretation and accompanying trait and state changes in physiology (e.g., nasal resistance, bronchial resistance, neuro-endocrine secretion, neuronal firing).

Causation for MCS is unexplored, although because of great concern for recall bias, case-control studies will be more suspect than usual. There has been a strong tendency to jump to physiologic studies when we did not know who we were studying. However, this has been somewhat useful as, based on careful clinical study with methods currently available, we know that significant neuro-behavioral abnormalities do not accompany the severe neuro-behavioral symptoms of most persons with clinical MCS (5, 17). It is unlikely that investigators will find such changes with similar methods in those less symptomatically afflicted. If and when we find central nervous system alterations in MCS, will they be due to initiating or triggering chemicals or to underlying characteristics of the individuals?

Federal government research agencies appear not to consider MCS and other unexplained symptom conditions (except perhaps CFS and more recently Gulf War Illness(es)) as high priorities. They are not powerful killers, and frequently, certainly in the case of MCS, someone's ox is being gored by the concept of the condition. On the other hand, the potential for significant morbidity and economic loss from MCS symptoms...
affecting 15 percent of a population of school and working age are huge. Whether or not this is a “dis-
ease,” it is an important public health problem and it
does not exist in a vacuum. For instance, the National
Academy of Sciences/Institute of Medicine has con-
vened a succession of committees to study unex-
plained symptoms in terms of Gulf War problems and
symptoms related to breast implants. At least in the
case of Gulf War symptoms, careful epidemiology has
been done to show us that compared with soldiers who
did not deploy to the Persian Gulf, those who deployed
had two- to threefold increases in symptoms, without
apparent medical explanations (18, 19). What we still
do not have agreement on is what lies beneath these
symptoms: which path(s) they are mediated by.
Kreutzer et al. (1) have taken an important step to
move the overlapping fields of MCS and medically
unexplained symptoms onto more epidemiologically
firm footing. There is a problem out there. We still do
not know what it is.

REFERENCES
reporting sensitivities to chemicals in a population-based sur-
2. Kroenke K, Mangelsdorff AD. Common symptoms in ambula-
tory care: incidence, evaluation, therapy, and outcome. Am J
3. Kroenke K, Spitzer RL, Williams JBW, et al. Physical symp-
toms in primary care—predictors of psychiatric disorders and
4. Buchwald D, Garrity D. Comparison of patients with chronic
fatigue syndrome, fibromyalgia, and multiple chemical sensi-
5. Fiedler N, Kipen HM, DeLuca J, et al. A controlled compari-
son of multiple chemical sensitivity and chronic fatigue syn-
6. Fiedler N, Kipen HM. Chemical sensitivity: the scientific lit-
erature. In: Experimental approaches to chemical sensitivity.
7. Spurgeon A, Gomertz D, Harrington JM. Modifiers of non-
specific symptoms in occupational and environmental syn-
8. Clauw DJ. The pathogenesis of chronic pain and fatigue syn-
dromes, with special reference to fibromyalgia. Med
of airway hyperresponsiveness in chronic stable asthma. J
chemical sensitivity prevalence. Am J Public Health
12. Kipen HM, Fiedler N, Lehrer P. Multiple chemical sensitivity:
 ultrastructure in patients with chronic airway inflammation
(RADS and RUDS) following an irritant exposure. Clin Tox
14. Leventhal EA, Crouch M. Are there differences in perceptions
of illness across the lifespan? In: Petrie KJ, Weinman JA, eds.
Perceptions of health and illness: current research and applica-
tions. Singapore: Harwood Academic Publications,
15. Anger WK. Worksite behavioral research: results, sensitive
methods, test batteries and the transition from laboratory data
16. Dick RB. Neurobehavioral assessment of occupationally rele-
sant solvents and chemicals in humans. In: Chang LW, Dyer
RS, eds. Handbook of neurotoxicology. New York: Marcel
chological and neuropsychological factors in multiple chemi-
18. The Iowa Persian Gulf Study Group. Self-reported illness and
health status among Gulf War veterans—a population-based
study. JAMA 1997;277:238–45.
symptom illness affecting Air Force veterans of the Gulf War.