

Environmental Factors in Medically Unexplained Symptoms and Related Syndromes: The Evidence and the Challenge

Howard M. Kipen and Nancy Fiedler

Environmental and Occupational Health Sciences Institute, University of Medicine and Dentistry of New Jersey—Robert Wood Johnson Medical School, Piscataway, New Jersey, USA

Symptoms, and especially those without clear underlying medical explanations, account for a large percentage of clinical encounters. Many unexplained symptoms have been organized by patients and practitioners into syndromes such as chronic fatigue syndrome, multiple chemical sensitivity, sick building syndrome, Gulf War syndrome, and the like. All these syndromes are defined solely on the basis of symptoms rather than by medical signs. Some of the above-described conditions overlap strongly with explained conditions such as asthma. The relationship of such symptoms and syndromes to environmental exposure is often sharply debated, as is the distinction between the various syndromes. This leads to problems of what type of research should be conducted and who should conduct it. It is time to develop a comprehensive research agenda to sort out nomenclature, epidemiology, and environmental causation for these conditions, moving toward comprehensive and effective public health and clinical approaches. *Key words:* asthma, environment, indoor air, psychology, research, symptoms. *Environ Health Perspect* 110(suppl 4):597–599 (2002). <http://ehpnet1.niehs.nih.gov/docs/2002/suppl-4/597-599kipen/abstract.html>

Symptoms

Symptoms, as reported by individuals to health providers, account for a high proportion of medical encounters, and a surprising majority are not explained by pathologic medical conditions. Examples of such physical symptoms that after evaluation are found to be without explanatory morphologic or laboratory findings include headache, fatigue, trouble concentrating, musculoskeletal symptoms, sleep problems, nausea, atypical chest pain, and shortness of breath (1,2). Rather than simply dismiss these unexplained symptoms or consider them as isolated symptoms, over the past few decades, practitioners, patients, and investigators have coalesced these symptoms into syndromes, including chronic fatigue syndrome (CFS), fibromyalgia (FM), chronic hypoglycemia, and irritable bowel syndrome. Similar and sometimes almost overlapping groups of symptoms have been delineated in the aftermath of a variety of ongoing chemical or other environmental exposures and include sick building syndrome (nonspecific building-related illness), atypical connective tissue disease after silicone breast implants, multiple chemical sensitivities (MCS), and most recently Gulf War syndrome and sensitivity to methyl *tert*-butyl ether (MTBE) (3). Investigators have pointed out the substantial overlap between one unexplained symptom classification and another, such that 30–50% of individuals with CFS, FM, and MCS qualify (based on self-reported symptoms) for at least one of the other diagnoses, and substantial percentages of those reporting illness after the Gulf War have symptom complexes overlapping with CFS and MCS (4–7). 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. For Gulf War veterans, where the absence of clinical pathology was explored with physical and laboratory exams on a population rather than case series basis, the absence of medical explanation was most clearly demonstrated without the biases inherent in selected samples (6). It is clearly impossible to accurately estimate costs of all such conditions; however, expenditures on research and treatment for all of these have been substantial. Limited literature addresses productivity effects related to indoor air (8,9). In its 1994 Indoor Air Quality proposal, the Occupational Safety and Health Administration estimated the productivity costs associated with poor indoor air quality at \$15 billion (10).

Psychological/Psychiatric Explanations

Psychiatric explanations and nomenclature have less than a perfect fit for many cases of unexplained somatic symptoms, not withstanding the significant (sometimes >50% for MCS and CFS) co-morbidity for anxiety and/or depression (5,11). To complicate assessments, some investigators have noted that the number of symptoms an individual reports is highly correlated with rates of anxiety and depression (2). The purest psychiatric diagnosis for an unexplained symptom syndrome is somatization disorder. However, many individuals who qualify for CFS and MCS do not qualify for somatization disorder based on existing criteria, and furthermore, variant definitions for somatization disorder have been explored (5,12,13).

A growing literature documents the association between environmental stimuli and symptoms that are not known to be

organically based (14,15). The most widely accepted example of this is that of post-traumatic stress disorder (PTSD), in which the experience of a traumatic environmental event is a prerequisite for the diagnosis and is the trigger for symptoms. PTSD has also been associated with environmental chemical exposures, as has the occurrence of other psychiatric disorders such as anxiety and depression (15,16). The association between environmental chemical exposures and unexplained physical symptoms, after adjusting for psychiatric distress, has also been reported but is less well accepted or understood (17).

Symptoms and the Environment

What is widely accepted, perhaps less so by the public than by the scientific and especially the mental health communities, is that there are many other determinants of symptoms than currently recognizable organic pathology. This was clearly described by Anne Spurgeon and her colleagues in a variant of the biopsychosocial model shown in Figure 1, which has two paths for symptoms, one somatic (biological) and the other a combination of psychological and sociological (15). Both paths are probably active in all individuals at all times, although new biological knowledge or new social phenomena can increase the relative importance attributed to either side for a given problem.

This model allows for three different elements to combine for the production of a symptomatic state. The first is a person with a biomedical condition or susceptibility such as airway hyperreactivity or vasomotor rhinitis. The second element is an exposure to a detectable, possibly irritating and/or odiferous but not significantly tissue-damaging in morphologic or biochemical terms, concentration of a stimulus or toxin. The third element is a person or group with one or more personal or group psychosocial risk factors for developing or reporting symptoms. With

This article is part of the monograph *Environmental Factors in Medically Unexplained Physical Symptoms and Related Syndromes*.

Address correspondence to H.M. Kipen, UMDNJ—Robert Wood Johnson Medical School, EOHSI—Occupational Health Division, 170 Frelinghuysen Rd., Piscataway, NJ 08854 USA. Telephone: (732) 445-0123, ext. 629. Fax: (732) 445-3644. E-mail: kipen@eohsi.rutgers.edu

Received 3 December 2001; accepted 20 June 2002.

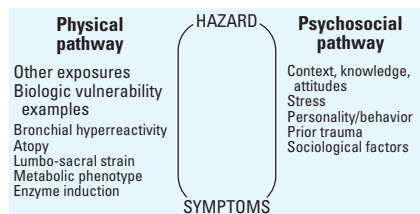


Figure 1. Modifiers of symptoms in occupational and environmental syndromes. Adapted from Spurgeon et al. (15).

these different elements interacting, it easy to see how different groups of investigators (and patients) differ as to on which side of a line of discrimination (psychological vs. physical) the various unexplained symptom syndromes related to environment lie. As explained above, there may also be more than one line, and an individual may simultaneously be appropriately characterized along more than one seemingly orthogonal axis. Research must help to sort out how we can simultaneously evaluate the relative contributions of each of the multiple paths to symptoms.

Neutra and colleagues considered this in a series of reports that address the higher symptom rates they observed around hazardous waste sites in California (18–20). Prevalence odds ratios for specific symptoms in exposed versus unexposed populations were significantly elevated more than 2-fold for 64% of symptoms assessed in one study, with fatigue, headache, poor sleep, nausea, chest pain, and others sometimes showing odds in the 5- to 10-fold range (18). They considered possible mechanisms for increased symptoms to include classical toxicity, an immunological or other physiogenic syndrome, behavioral sensitization, psychosomatic reaction to stress, mass psychogenic illness, reporting bias, confounding factors, or odor, as an effect modifier. They noted the demonstrated excess of symptoms in other situations (Three Mile Island, anticipated insecticide spraying) where exposure to toxic agents essentially did not occur and the symptoms were, on reflection, due to “environmental anxiety.” They concluded for the dump sites that classical toxicity was unlikely to explain the symptoms and noted that many more symptoms occurred in those who complained of odors in combination with having a high degree of “environmental worry.” They felt it was possible that autonomic, stress-mediated mechanisms or behavioral sensitization could have been active in the genesis of the symptoms. In a follow-up analysis, Shusterman et al. (19) found an interaction between environmental worry and odor perception frequency, in addition to their independent effects, such that headaches were reported 38 times as often among those with high worry and frequent odor perception. It was hypothesized that odors may serve

as a sensory cue for the manifestation of stress-related illness or heightened awareness of underlying symptoms among individuals concerned about the quality of their neighborhood environment. Experimental support for an interaction between perception of chemical odors and development of symptoms has been reported: when a situation was manipulated to suggest that an odor may be harmful, more symptoms were reported by subjects than when neutral or positive cues accompanied the same odor in the same setting (21).

Epidemiology

A study published in the *American Journal of Epidemiology* showed that symptoms associated with chemical sensitivity are fairly prevalent in the general population, are more severe in asthmatic individuals, and have a variable relationship to disability and medical diagnosis (22). Very surprising were the magnitude of the general prevalence of sensitivity to chemicals (15%), the frequency of reported physician diagnosis of MCS or environmental illness (6%), 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 Centers for Disease Control and Prevention’s rigorously conducted and randomly sampled Behavioral Risk Factor Surveillance interview series makes these data highly reliable and generalizable. Another recent study quantifies an increased burden of disability in Gulf War veterans meeting one definition for MCS (23).

A number of recent investigations from both the United States and the United Kingdom have documented in well-designed population-based studies that soldiers who were deployed to the Gulf War zone experienced 2 to 3 times the rate of symptoms as comparable soldiers not deployed to the Gulf War zone, and that there were no apparent medically diagnosable conditions to explain this symptomatology (6,24–26). Concern for toxicologic causes of their symptoms remains exceedingly high, as demonstrated by the extensive mainstream press coverage in October 1999 given to a RAND literature review that concluded that pyridostigmine bromide may have caused some of the symptoms (27). A recent study suggested an increased risk for multiple symptoms among those U.K. soldiers who received multiple vaccines during deployment but not for those similarly vaccinated before deployment, perhaps suggesting some interesting possibilities for psychoneuroimmunological interactions (28).

Mechanistic Implications and Complications

Ultimately, if we have experimentally validated mechanisms to explain the symptoms,

we will greatly advance our competence at differential diagnosis, as well as opportunities for prevention and treatment. Some investigators are beginning to uncover potentially relevant biological differences between those who suffer with unexplained symptom syndromes and those who do not. Among examples of this is the finding of elevated substance P levels in the cerebrospinal fluid of those with clinical FM (29). Although all behavior and symptomatology are at some level grounded in physiologic brain function at a neurochemical level, 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, anxiety) and those diagnosed dominantly by physiology (e.g., seizure disorders, multiple sclerosis) (30).

In a random sample of Californians, one in five asthmatics reported being told by his/her physician that he/she had environmental illness or MCS; this is highly consistent with previous studies suggesting that at least the symptoms of people diagnosed with the two conditions (asthma and MCS) are often difficult to discriminate (31–33). However, because for asthma we have reasonably well validated markers for the condition (e.g., bronchial hyperreactivity as measured by nonspecific challenge or by response to bronchodilator medication), the differential diagnosis is less vexing than with symptoms such as fatigue, headache, or trouble concentrating. The last symptom is very common and often seems severe and disabling. On the basis of careful clinical study with neuro-behavioral methods currently available, we know that significant and measurable neuro-cognitive abnormalities do not accompany the severe neurocognitive symptoms of most with clinical MCS or CFS (5,34). It is unlikely that investigators will find such changes with similar methods in patients who are less symptomatically afflicted than in the rather extremely afflicted subjects studied in these two groups.

An important study by Meggs et al. (35) surveyed a random sample of rural North Carolinians by telephone, and with a 71% response rate found 35% reported sickness after smelling chemical odors (chemical sensitivity) and 35% reported sickness after smelling “natural things” (allergy), with 16.9% reporting both kinds of response. The respective roles of the concept of immunoglobulin E allergy, irritancy, and airway (upper and lower) reactivity in these percentages needs to be apportioned in any adequate nosology of how medically unexplained physical symptoms relate to the environment.

Additionally, many more theories to explain how individuals might become sensitive to low levels of chemicals have been

advanced. Because human experimental data are limited for all of them, they are not discussed extensively in the present report, but excellent reviews are available (36,37). Extensive discussions are beyond the scope of the present article.

Challenges

In general, we still need accepted and validated definition(s) for various presentations of symptomatic complaints stemming from environmental exposures. Defining severity and disability needs more focused exploration. We rarely know what we are looking at in biological terms. If some of these symptoms are actually preferences to be protected from certain olfactory stimuli (scents) rather than documented pathology, how do they fit into health? In a model reliant on disease, they would not qualify. However, if the broader World Health Organization definition of health as complete physical, mental, and social well-being is used, such preferences might well become drivers of preventive action (38). In the traditional paradigm of occupational and environmental medicine, we were concerned with the question, What is the cause of this illness? The prevalence of medically unexplained physical symptoms raises newer but more frequently occurring and fundamental questions: Is this illness? What is the apportionment of this illness between the biological and the psychological? Specific recommendations are in the accompanying review of the results of the conference (39).

Federal government health and research agencies appear not to consider MCS and other unexplained symptom conditions (except perhaps CFS and more recently Gulf War syndrome) as significant priorities. After years of effort, an interagency report on MCS remains a predecisional draft, unissued (40). These conditions are not powerful killers, and frequently, because someone's ox is being gored by the concept of a cause for the condition, there is overt opposition to recognition (definition) of the problem. This is, of course, facilitated by the definitional difficulties referred to above. On the other hand, the potential for significant morbidity and economic loss from symptoms such as those of MCS, affecting 15% of a population of school and working age, is huge (22). Whether or not these conditions are "diseases," they represent significant public health problems and are often not readily distinguished from more clearly organic conditions.

The National Academy of Sciences and the Institute of Medicine have convened a succession of committees to study unexplained symptoms in terms of Gulf War issues. As explained above, careful epidemiology shows

that, compared with soldiers who did not deploy to the Persian Gulf, those who deployed had 2- to 3-fold increases in symptoms, without apparent medical explanations (6,26). However, we still do not have agreement on what lies beneath these symptoms or what path(s) mediate them. Clearly there is a public health problem, and denial of its significance and magnitude will not bring us closer to managing its consequences.

The following companion article (39) to this introduction to the problem summarizes the results of contributed papers and group discussions raised in the present discussion.

REFERENCES AND NOTES

- Kroenke K, Mangelsdorff AD. Common symptoms in ambulatory care: incidence, evaluation, therapy, and outcome. *Am J Med* 86:262–266 (1989).
- Kroenke K, Spitzer RL, Williams JBW, Linzer M, Hahn SR, deGruy FV, Brody D. Physical symptoms in primary care—predictors of psychiatric disorders and functional impairment. *Arch Fam Med* 3:774–779 (1994).
- Fiedler N, Kelly-McNeil K, Mohr S, Lehrer P, Opiekun R, Lee CW, Wainman T, Hamer R, Weisel C, Edelberg R, et al. Controlled human exposure to methyl tertiary butyl ether in gasoline: symptoms, psychophysiological and neurobehavioral responses of self-reported sensitivities. *Environ Health Perspect* 108:753–763 (2000).
- Buchwald D, Garrity D. Comparison of patients with chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivities. *Arch Intern Med* 154:2049–2053 (1994).
- Fiedler N, Kipen HM, DeLuca J, Kelly-McNeil K, Natelson B. A controlled comparison of multiple chemical sensitivity and chronic fatigue syndrome. *Psychosom Med* 58:38–49 (1996).
- Fukuda K, Nisenbaum R, Stewart G, Thompson WW, Robin L, Washko RM, Noah DL, Barrett DH, Randall B, Herwaldt BL, et al. Chronic multisymptom illness affecting Air Force veterans of the Gulf War. *JAMA* 280:981–988 (1998).
- Kipen H, Hallman W, Kang HK, Fiedler N, Natelson BH. Prevalence of chronic fatigue and chemical sensitivities in Gulf Registry veterans. *Arch Environ Health* 54(5):313–318 (1999).
- Milton DK, Glencross PM, Walters MD. Risk of sick leave associated with outdoor air supply rate, humidification, and occupant complaints. *Indoor Air* 10(4):212–221 (2000).
- Wargocki P, Wyon DP, Sundell J, Clausen G, Fanger PO. The effects of outdoor air supply rate in an office on perceived air quality, sick building syndrome (SBS) symptoms and productivity. *Indoor Air* 10(4):222–236 (2000).
- OSHA. Indoor air quality. Federal Reg 59:15968–16039 (1994).
- Fiedler N, Kipen H. Chemical sensitivity: the scientific literature. *Environ Health Perspect* 105:409–415 (1997).
- Johnson SK, DeLuca J, Natelson BH. Assessing somatization disorder in the chronic fatigue syndrome. *Psychosom Med* 58:50–57 (1996).
- Escobar JI, Hoyos-Nervi C, Gara M. Medically unexplained physical symptoms in medical practice: a psychiatric perspective. *Environ Health Perspect* 110(suppl 4):631–636 (2002).
- Bowler R, Mergler D, Huel G, Cone JE. Adverse health effects in African American residents living adjacent to chemical industries. *J Black Psychol* 22:470–497 (1996).
- Spurgeon A, Gompertz D, Harrington JM. Modifiers of non-specific symptoms in occupational and environmental syndromes. *Occup Environ Med* 53:361–366 (1996).
- Bowler R, Ngo L, Hartney C. Amnesic disturbance and PTSD after chemical release. *Arch Clin Neuro* 13(5):445–471 (1998).
- Proctor SP, Heeren T, White RF, Wolfe J, Borgos MS, Davis JD, Pepper L, Clapp R, Sutker PB, Vasterling JJ, et al. Health status of Persian Gulf War veterans: self-reported symptoms, environmental exposures and the effect of stress. *Int J Epidemiol* 27:1000–1010 (1998).
- Lipscomb J, Goldman LR, Satin K, Smith D, Vance W, Neutra R. A follow-up study of the community near the McColl waste disposal site. *Environ Health Perspect* 94:15–24 (1991).
- Shusterman D, Lipscomb J, Neutra R, Satin K. Symptom prevalence and odor-worry interaction near hazardous waste sites. *Environ Health Perspect* 94:25–30 (1991).
- Neutra R, Lipscomb J, Satin K, Shusterman D. Hypotheses to explain the higher symptom rates observed around hazardous waste sites. *Environ Health Perspect* 94:31–38 (1991).
- Dalton P. Cognitive influences on health symptoms from acute chemical exposure. *Health Psychol* 18:579–590 (1999).
- Kreutzer R, Neutra RR, Lashuay N. Prevalence of people reporting sensitivities to chemicals in a population-based survey. *Am J Epidemiol* 150(1):1–12 (1999).
- Black DW, Doebbeling BN, Voelker MD, Clarke WR, Woolson RF, Barrett DH, Schwartz DA. Quality of life and health-services utilization in a population-based sample of military personnel reporting multiple chemical sensitivities. *J Occup Environ Med* 41:928–933 (1999).
- Hodgson MJ, Kipen H. Gulf War illnesses: causation and treatment. *J Occup Environ Med* 41:443–452 (1999).
- Unwin C, Blatchley N, Coker W, Ferry S, Hotopf M, Hull L, Ismail K, Palmer I, David A, Wessely S. Health of UK servicemen who served in Persian Gulf War. *Lancet* 353:169–178 (1999).
- The Iowa Persian Gulf Study Group. Self-reported illness and health status among Gulf War veterans—a population-based study. *JAMA* 277:238–245 (1997).
- Golomb BA. Pyridostigmine Bromide. A Review of the Scientific Literature as It Pertains to Gulf War Illnesses. Washington, DC:RAND, 1999.
- Hotopf M, David A, Hull L, Ismail K, Unwin C, Wessely S. Role of vaccinations as risk factors for ill health in veterans of the Gulf War: cross sectional study. *Br Med J* 320:1363–1367 (2000).
- Claw DJ. The pathogenesis of chronic pain and fatigue syndromes, with special reference to fibromyalgia. *Med Hypoth* 44:369–378 (1995).
- Kandel ER. A new intellectual framework for psychiatry. *Am J Psychiatr* 155:457–469 (1998).
- Brooks SM, Bernstein L, Raghuprasad PK, Maccia CA, Mieczkowski L. Assessment of airway hyperresponsiveness in chronic stable asthma. *J Allergy Clin Immunol* 85:17–26 (1990).
- Kipen HM, Hallman W, Kelly-McNeil K, Fiedler N. Measuring chemical sensitivity prevalence: a questionnaire for population studies. *Am J Public Health* 85:574–577 (1995).
- Kipen HM, Fiedler N, Lehrer P. Multiple chemical sensitivity: a primer for pulmonologists. *Clin Pulm Med* 4:76–84 (1997).
- Simon GE, Daniell W, Stockbridge HL, Claypoole K, Rosenstock L. Immunologic, psychological, and neuropsychological factors in multiple chemical sensitivity. *Ann Int Med* 19:97–103 (1993).
- Meggs WJ, Dunn KA, Bloch RM, Goodman PE, Davidoff AL. Prevalence and nature of allergy and chemical sensitivity in a general population. *Arch Environ Health* 51(4):275–82 (1996).
- Sparks PJ, Daniell W, Black DW, Kipen HM, Altman LC, Simon GE, Terr AI. Multiple chemical sensitivity syndrome: a clinical perspective. I: Case definition, theories of pathogenesis, and research needs. *J Occup Med* 36(7):718–730 (1994).
- Graveling RA, Pilkington A, George JPK, Butler MPS, Tannahill N. A review of multiple chemical sensitivity. *Occup Environ Med* 56:73–85 (1999).
- World Health Organization. Definition of Health. Available: <http://www.who.int/about/who/en/definition.html> [accessed 19 June 2002].
- Kipen HM, Fiedler N. The role of environmental factors in medically unexplained symptoms and related syndromes: conference summary and recommendations. *Environ Health Perspect* 110(suppl 4):591–595 (2002).
- ATSDR. The Interagency Workgroup on Multiple Chemical Sensitivity. A Report on Multiple Chemical Sensitivity (MCS). Atlanta, GA:Agency for Toxic Substances and Diseases Registry, 1998.