Review Article

Chemical Sensitivity: Pathophysiology or Pathopsychology?

Stephen J. Genuis, MD

Faculty of Medicine, University of Alberta, Edmonton, Alberta, Canada

ABSTRACT

Background: Escalating numbers of people throughout the world are presenting to primary care physicians, allergists, and immunologists with myriad clinical symptoms after low-level exposure to assorted everyday chemicals such as smoke, perfumes, air fresheners, paints, glues, and other products. This clinical state is referred to by various diagnostic labels, including multiple chemical sensitivity disorder, environmental intolerance, chemical sensitivity (CS), and sensitivity-related illness, and has been the subject of much controversy within the health care community.

Objective: The goal of this study was to provide a brief overview of the etiology, pathogenesis, clinical presentation, and management of CS. An evaluation of the medical community's response to this emerging diagnosis was also explored.

Methods: This review was prepared by assessing available medical and scientific literature from MEDLINE, as well as by reviewing numerous books, toxicology journals, conference proceedings, government publications, and environmental health periodicals. A primary observation, however, is that there is limited scientific literature available on the issue of CS. The format of a traditional integrated review was chosen because such reviews play a pivotal role in scientific research and professional practice in medical issues with limited primary study and uncharted clinical territory.

Results: The sensitization state of CS seems to be initiated by a significant toxic exposure, occurring as a 1-time event, or on surpassing a threshold of toxicity after toxicant accrual from repeated lower-level exposures. Once sensitized through a toxicant-induced loss of tolerance, individuals exposed to inciting triggers such as minute amounts of diverse everyday chemicals may experience various clinical and immune sequelae, sometimes involving lymphocyte, antibody, or cytokine responses. Precautionary avoidance of inciting triggers will prevent symptoms, and desensitization immunotherapy or immune suppression may improve symptoms in some cases. Sustained resolution of the CS state occurs after successful elimination of the accrued body burden of toxicants through natural mechanisms of toxicant bioelimination and/or interventions of clinical detoxification. Despite extensive clinical evidence to support the veracity of this clinical state, many members of the medical community are reluctant to accept this condition as a pathophysiologic disorder.

Conclusions: The emerging problem of ubiquitous adverse toxicant exposures in modern society has resulted in escalating numbers of individuals developing a CS disorder. As usual in medical history, iconoclastic ideas and emerging evidence regarding novel disease mechanisms, such as the pathogenesis of CS, have been met with controversy, resistance, and sluggish knowledge translation. (*Clin Ther.* 2013;35:572–577)

Key words: chemical sensitivity, clinical detoxification, environmental intolerance, multiple chemical sensitivity disorder, sensitivity-related illness, toxicant-induced loss of tolerance.

> *Predetermined politicized positions are precisely what science supposedly repudiates.*
>
> *-Matthew Hanley*

INTRODUCTION

Food intolerance and chemical sensitivity (CS) were seemingly infrequent problems in society 50 years ago. Currently, however, an increasing proportion of the pediatric and adult population in the developed world experiences adverse reactions elicited by exposure to low concentrations of not only antigenic stimuli such as foods or inhalants but also to chemicals that are well

Accepted for publication April 11, 2013.
http://dx.doi.org/10.1016/j.clinthera.2013.04.003
0149-2918/$ - see front matter

tolerated by the majority. Furthermore, not all such sensitivity reactions represent the classically understood concept of "allergic" phenomenon involving immunoglobulin(Ig) E antibody-mediated response. The occurrence of alleged hyperreactivity to diverse everyday chemical incitants, sometimes referred to as multiple chemical sensitivity or just CS, now seems to seriously affect ~3% to 4% of the general population, including children,[1,2] and has become an increasing public health dilemma[3] in many jurisdictions throughout the globe.[2,4–6]

As is common with heretofore unexplained conditions, patients presenting with CS have been received unsympathetically by some medical practitioners.[7] Often thought to be a manifestation of disordered psychology, many researchers and clinicians have rejected CS as a pathophysiologic condition. Some have welcomed the forthcoming American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fifth Revision*, diagnosis of somatic symptoms disorder[8] as a fitting diagnostic category for attribution of this clinical presentation. A mounting body of evidence, however, suggests that the millions of individuals suffering from this apparently new CS disorder have common features and may have a common etiology. This brief review provides an introduction to the baffling condition of CS.

RESULTS

Etiology of CS States

Over the last 50 years, our culture has experienced an unprecedented chemical revolution with the manufacture and release of myriad synthetic chemical agents into our homes, workplaces, and schools.[9] Major medical bodies such as the Centers for Disease Control and Prevention have established that many people in the population maintain a toxicant burden.[10] Considerable evidence has linked diverse health concerns to intense, acute exposure, as well as to repeated low-level exposure, to potentially toxic agents.[9] It is noteworthy that many observational studies have found that assorted types of toxicant exposure, including chemicals and biologic agents such as mold, generally precede the development of CS states.[11] Furthermore, the epidemiologic escalation of CS in the general population parallels the rising prevalence of toxicant exposures by population groups.

Individuals occupationally exposed to various adverse agents, for example, have an increased prevalence of CS,[12,13] with major differences between exposed versus nonexposed employees within the same occupation.[12] Many articles discuss the initiation of sensitivity issues after contaminated air exposure within building settings.[14–19] Following the 9/11 disaster and recent warfare such as the conflict in the Persian Gulf, many participants working in toxicant replete milieus subsequently developed CS states that were non-existent before the exposures.[20–24] Newly established CS was also documented in many survivors of the 1984 Bhopal industrial catastrophe after their exposure to various toxins released by a pesticide plant.[25] In research settings, it is possible to induce sensitivity states in animals by exposing them to toxic insults.[26–28]

It thus seems that exogenous toxic exposures initiate a hypersensitive immune state, whereby the immune response subsequently becomes dysregulated with a consequent toxicant-induced loss of tolerance[29] to minute exposures of compounds such as diverse chemicals. (**Figure**) The degree of hypersensitivity is dynamic and appears to parallel the scale of the total body burden of bioaccumulated toxicants. A clinical outcome ensues in which these minute exposures to

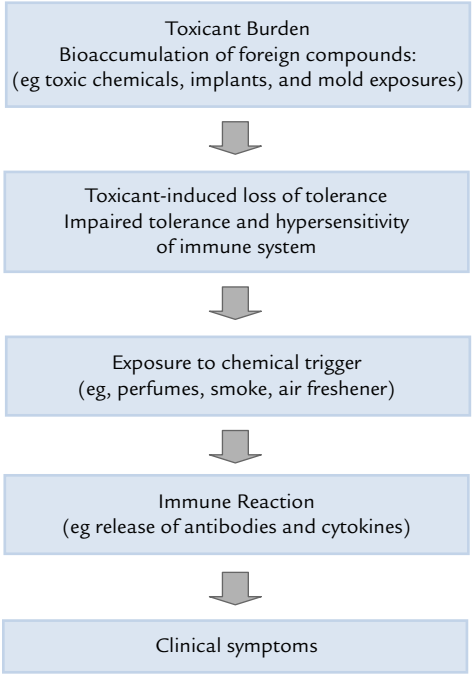

Figure. Mechanism of development of chemical sensitivity.

assorted incitants such as myriad chemicals-potentially including everyday scented products like smoke, perfumes, air fresheners, paints, and glues as well as assorted non-scented agents such as some pesticides, non-stick agents, radon and emissions from particle board-evoke diverse signs and symptoms,[30,31] an outcome referred to as CS.

Immunogenic Pathogenesis of CS

Speculation regarding the precise immunogenic pathogenesis of CS continues to unfold, including the hypothesis that cytokines released in association with exposure events[32] directly induce a sensitization effect on the immune system through induced dysregulation.[33] The consequent response to low-dose stimuli and resulting inflammation may be triggered by a reflex mechanism that initiates an inflammatory immune reaction,[34] perhaps through varied immune cells and their byproducts.

Support for this perspective includes observation of cytokine changes in response to some chemical and biological triggers.[32,35] Urban air particulate matter, for example, has been associated with a proinflammatory cytokine response in some individuals,[36,37] and bacterial contamination of indoor air has been found to stimulate cytokine release in vivo.[35] Inflammatory cytokines have been found in the nasal passages and lungs of individuals exposed to some toxicants,[38,39] which might explain the various respiratory and other common symptoms in CS. Immune responses can vary, as a recent study demonstrated that some chemical triggers evoke changes in IgE and Th2 cytokines whereas different chemicals elicit a Th1 cytokine response with no elevation of serum IgE.[1]

Metabolic parameters suggest accelerated lipid oxidation, increased nitric oxide production, and glutathione depletion in conjunction with increased plasma inflammatory cytokines in many individuals with CS.[40] Because assorted cytokines maintain the immunomodulating ability to effect inflammation as well as cell-to-cell signaling, it is theorized that in some individuals with CS, various stimuli may trigger a host of varied cytokines or a "cytokine storm," which can result in dysregulated cell signaling, biochemical disruption, and inflammation with resulting clinical manifestations in various organ systems.[41,42]

Clinical States Associated With CS

Patients with CS may present with chemical intolerance in isolation or, more commonly, with a long list of inexplicable health issues. Because CS is often part of a constellation of conditions referred to as sensitivity-related illness (SRI),[30,40] intolerance of some foods, inhalants, biologic compounds (eg, molds), and/or chemicals may coexist. Differing types of underlying exposures confronting unique genomes and biochemistry could account for the marked variation in clinical presentation and immune response. As a result, manifestations of CS are diverse and can involve many organ systems.[17,30]

Although delayed reactions are reported, signs and symptoms of CS usually occur within minutes to an hour after incitant exposure. The reactions range from mild (eg, slight headache, sneezing, rash, dizziness) to more severe (eg, incapacitating fatigue, pain, weakness, intestinal symptoms, heart palpitations, panic attacks, migraines, depression).[2] The severity of morbidity may relate to the intensity of the initiating toxic burden as well as to the exposure dose of subsequent incitants. Various authors have reported that the most common symptoms associated with CS include fatigue, muscle aches, memory and concentration difficulties, anxiety, gastrointestinal problems, and headache.[43,44] There are, however, many other multisystem signs and symptoms that may be the direct result of CS. Presenting features of fatigue and musculoskeletal discomfort account for the overlap with diagnoses such as chronic fatigue syndrome and fibromyalgia, syndromes that can, in some cases, also be the result of toxicant burdens.

CS is a condition that may commence abruptly or gradually in previously healthy susceptible individuals.[3,17,31] It can start at any stage of life as a direct consequence of adverse exposure but is eminently modifiable with appropriate therapeutic intervention.[30]

Clinical Therapeutic Approach

Many therapies have been tried, with varying results, to address the problem of CS.[45] Symptomatic desensitization immunotherapies aimed at preempting the hypersensitivity immune response associated with exposure in susceptible individuals are being used.[46] Desensitization immunotherapy is typically achieved by injecting or sublingually applying microdoses of the trigger substance that, by uncertain mechanisms, may turn off or preclude hyperreactive responses to incitants; this method may induce a state of desensitization whereby the immune response to specific chemical antigens is blunted.[46–48] Intradermal skin testing by challenging with potential antigens is sometimes used to delineate specific chemical triggers.

Steroids may also suppress immune hyperactivity and mitigate the hypersensitive response. The efficacy of steroids and other immunosuppressants in a variety of seemingly unrelated conditions may signify that SRI is a common pathophysiologic mechanism of clinical illness in many organ systems. With potential adverse effects, long-term health risks, and failure to address the etiology of CS, ongoing steroid use is not a preferred therapeutic approach. Cognitive therapy and neural retraining are being explored as treatment options for CS,[49,50] but psychotherapeutic interventions have thus far not met with much reliable success.[45] Some patients choose to withdraw from society and become "21st century hermits" to avoid chemical triggers,[51] as 95% of CS respondents in 1 study claim that chemical avoidance and creating a chemical-free living space are consistently helpful.[45]

In general, physiologic treatments consistently seem to have superior and sustained outcomes compared with psychological therapies. The preferred medical management of CS, designed to restore persistent health and freedom from SRI, involves elimination of the initiating body burden of primary toxicants.[30] The purging of the underlying toxicant burden through innate mechanisms of toxicant elimination or through clinical detoxification interventions for persistent pollutants[52,53] seems to consistently diminish the immune dysregulation associated with CS and to gradually ameliorate the clinical manifestations of CS.[30]

CONCLUSIONS

Although some degree of CS reportedly now occurs in up to 1 in 5 primary care patients presenting with diverse symptoms, this condition is rarely recognized by clinicians.[54] As has occurred with many disorders in the past, including Parkinson's disease, asthma, ulcerative colitis, migraine headaches, multiple sclerosis, autism, and other clinical entities,[11] many scientists have been reluctant to accept CS as a pathophysiologic disorder. However, emerging evidence continues to substantiate that significant exogenous exposures initiate a hypersensitive immune state, whereby the immune system becomes dysregulated with resulting impaired tolerance to minute exposures of foreign antigens, including chemicals. In response to such evidence, various governments have formally recognized the veritable diagnosis of CS,[55] and increasing dialogue regarding CS has been generated in the legal community.[56] As a preventable and reversible condition, CS requires public health attention to preclude toxicant exposures[55] and informed clinical care to alleviate the suffering associated with CS and to preempt the potential chronicity of this disorder.

ACKNOWLEDGMENT

The author thanks Dr. Margaret E. Sears for kindly reviewing the manuscript. Dr. Genuis was responsible for the literature search, data interpretation, figure creation, and writing of the manuscript.

CONFLICTS OF INTEREST

The author has indicated that he has no conflicts of interest regarding the content of this article.

REFERENCES

1. Fukuyama T, Ueda H, Hayashi K, et al. Detection of low-level environmental chemical allergy by a long-term sensitization method. *Toxicol Lett*. 2008;180:1–8.
2. Miller CS, Ashford NA. Multiple chemical intolerance and indoor air quality. In: Spengler JD, Samet JM, McCarthy JF, eds. *Indoor Air Quality Handbook*. New York, NY: McGraw-Hill; 2000.
3. Pall ML. Multiple Chemical Sensitivity: Toxicological Questions and Mechanisms. In: Ballantyne B, Marrs TC, and Syversen T, eds. *General and Applied Toxicology*. 3rd ed. Chichester, West Sussex, UK: John Wiley & Sons; 2009.
4. Berg ND, Linneberg A, Dirksen A, Elberling J. Prevalence of self-reported symptoms and consequences related to inhalation of airborne chemicals in a Danish general population. *Int Arch Occup Environ Health*. 2008;81:881–887.
5. Hausteiner C, Bornschein S, Hansen J, et al. Self-reported chemical sensitivity in Germany: a population-based survey. *Int J Hyg Environ Health*. 2005;208:271–278.
6. Johansson A, Bramerson A, Millqvist E, et al. Prevalence and risk factors for self-reported odour intolerance: the Skovde population-based study. *Int Arch Occup Environ Health*. 2005;78:559–564.
7. Gibson PR, Lindberg A. Physicians' perceptions and practices regarding patient reports of multiple chemical sensitivity. *ISRN Nurs*. 2011;2011:838930.
8. American Psychiatric Association. DSM-5 Development. Somatic symptoms disorders. http://www.dsm5.org/MeetUs/Pages/SomaticDistressDisorders.aspx. Accessed February 21, 2013.
9. Genuis SJ. The chemical erosion of human health: adverse environmental exposure and in-utero pollution—determinants of congenital disorders and chronic disease. *J Perinat Med*. 2006;34:185–195.

10. Centers for Disease Control, Department of Health and Human Services. Fourth National Report on Human Exposure to Environmental Chemicals. http://www.cdc.gov/exposurereport/pdf/FourthReport.pdf. Accessed January 18, 2009.
11. Pall ML. *Explaining "Unexplained Illness": Disease Paradigm for Chronic Fatigue Syndrome, Multiple Chemical Sensitivity, Fibromyalgia; Post-Traumatic Stress Disorder, Gulf War Syndrome and Others*. New York, NY: Harrington Park Press; 2007.
12. Zibrowski EM, Robertson JM. Olfactory sensitivity in medical laboratory workers occupationally exposed to organic solvent mixtures. *Occup Med (Lond)*. 2006;56:51–54.
13. Yu IT, Lee NL, Zhang XH, et al. Occupational exposure to mixtures of organic solvents increases the risk of neurological symptoms among printing workers in Hong Kong. *J Occup Environ Med*. 2004;46:323–330.
14. Welch LS, Sokas R. Development of multiple chemical sensitivity after an outbreak of sick-building syndrome. *Toxicol Ind Health*. 1992;8:47–50.
15. Simon GE, Katon WJ, Sparks PJ. Allergic to life: psychological factors in environmental illness. *Am J Psychiatry*. 1990;147:901–906.
16. Gordon M. Reactions to chemical fumes in radiology departments. *Radiography*. 1987;53:85–89.
17. Ashford N, Miller C. *Chemical Exposures: Low Levels and High Stakes*. 2nd ed. New York, NY: John Wiley and Sons; 1998.
18. Lax MB, Henneberger PK. Patients with multiple chemical sensitivities in an occupational health clinic: presentation and follow-up. *Arch Environ Health*. 1995;50:425–431.
19. Miller CS, Mitzel HC. Chemical sensitivity attributed to pesticide exposure versus remodeling. *Arch Environ Health*. 1995;50:119–129.
20. Bell IR, Walsh M, Gross A, et al. Cognitive dysfunction and disability in geriatric veterans with self-reported intolerance to environmental chemicals. *J Chronic Fatigue Syndrome*. 1997;3:15–42.
21. Fukuda K, Nisenbaum R, Stewart G, et al. Chronic multisymptom illness affecting Air Force veterans of the Gulf War. *JAMA*. 1998;280:981–988.
22. Fiedler N, Giardino N, Natelson B, et al. Responses to controlled diesel vapor exposure among chemically sensitive Gulf War veterans. *Psychosom Med*. 2004;66:588–598.
23. Fiedler N, Kipen H, Natelson B, Ottenweller J. Chemical sensitivities and the Gulf War: Department of Veterans Affairs Research Center in basic and clinical science studies of environmental hazards. *Regul Toxicol Pharmacol*. 1996;24:S129–S138.
24. Reid S, Hotopf M, Hull L, et al. Reported chemical sensitivities in a health survey of United Kingdom military personnel. *Occup Environ Med*. 2002;59:196–198.
25. Nemery B. Late consequences of accidental exposure to inhaled irritants: RADS and the Bhopal disaster. *Eur Respir J*. 1996;9:1973–1976.
26. Rogers WR, Miller CS, Bunegin L. A rat model of neurobehavioral sensitization to toluene. *Toxicol Ind Health*. 1999;15:356–369.
27. Overstreet DH, Miller CS, Janowsky DS, Russell RW. Potential animal model of multiple chemical sensitivity with cholinergic supersensitivity. *Toxicology*. 1996;111:119–134.
28. Sorg BA, Hochstatter T. Behavioral sensitization after repeated formaldehyde exposure in rats. *Toxicol Ind Health*. 1999;15:346–355.
29. Miller CS. Are we on the threshold of a new theory of disease? Toxicant-induced loss of tolerance and its relationship to addiction and abdiction. *Toxicol Ind Health*. 1999;15:284–294.
30. Genuis SJ. Sensitivity-related illness: the escalating pandemic of allergy, food intolerance and chemical sensitivity. *Sci Total Environ*. 2010;408:6047–6061.
31. Miller CS. Toxicant-induced loss of tolerance—an emerging theory of disease? *Environ Health Perspect*. 1997;105(Suppl 2):445–453.
32. Duramad P, Tager IB, Holland NT. Cytokines and other immunological biomarkers in children's environmental health studies. *Toxicol Lett*. 2007;172:48–59.
33. Rowat SC. Integrated defense system overlaps as a disease model: with examples for multiple chemical sensitivity. *Environ Health Perspect*. 1998;106(Suppl 1):85–109.
34. Tracey KJ. Reflex control of immunity. *Nat Rev Immunol*. 2009;9:418–428.
35. Hirvonen MR, Huttunen K, Roponen M. Bacterial strains from moldy buildings are highly potent inducers of inflammatory and cytotoxic effects. *Indoor Air*. 2005;15(Suppl 9):65–70.
36. Jalava PI, Salonen RO, Pennanen AS, et al. Effects of solubility of urban air fine and coarse particles on cytotoxic and inflammatory responses in RAW 264.7 macrophage cell line. *Toxicol Appl Pharmacol*. 2008;229:146–160.
37. Jalava PI, Hirvonen MR, Sillanpaa M, et al. Associations of urban air particulate composition with inflammatory and cytotoxic responses in RAW 246.7 cell line. *Inhal Toxicol*. 2009;21:994–1006.
38. Hirvonen MR, Nevalainen A, Makkonen N, et al. Induced production of nitric oxide, tumor necrosis factor, and interleukin-6 in RAW 264.7 macrophages by streptomycetes from indoor air of moldy houses. *Arch Environ Health*. 1997;52:426–432.
39. Hirvonen MR, Ruotsalainen M, Roponen M, et al. Nitric oxide and proinflammatory cytokines in nasal lavage fluid associated with symptoms and exposure to moldy building microbes. *Am J Respir Crit Care Med*. 1999;160:1943–1946.
40. De Luca C, Scordo MG, Cesareo E, et al. Biological definition of mul-

tiple chemical sensitivity from redox state and cytokine profiling and not from polymorphisms of xenobiotic-metabolizing enzymes. *Toxicol Appl Pharmacol*. 2010; 248:285–292.
41. Tracey KJ. Physiology and immunology of the cholinergic antiinflammatory pathway. *J Clin Invest*. 2007;117: 289–296.
42. Czura CJ, Tracey KJ. Autonomic neural regulation of immunity. *J Intern Med*. 2005;257:156–166.
43. Gibson PR, Vogel VM. Sickness-related dysfunction in persons with self-reported multiple chemical sensitivity at four levels of severity. *J Clin Nurs*. 2009;18:72–81.
44. Sorg BA. Multiple chemical sensitivity: potential role for neural sensitization. *Crit Rev Neurobiol*. 1999;13: 283–316.
45. Gibson PR, Elms AN, Ruding LA. Perceived treatment efficacy for conventional and alternative therapies reported by persons with multiple chemical sensitivity. *Environ Health Perspect*. 2003;111:1498–1504.
46. Rea WJ. *Chemical Sensitivity: (Volume 4): Tools of Diagnosis and Methods of Treatment*. Boca Raton, Fla: Lewis Publishers; 1997.
47. Nowak-Wegrzyn A, Sicherer SH. Immunotherapy for food and latex allergy. *Clin Allergy Immunol*. 2008;21: 429–446.
48. Helms DJ, Mosure DJ, Secor WE, Workowski KA. Management of trichomonas vaginalis in women with suspected metronidazole hypersensitivity. *Am J Obstet Gynecol*. 2008; 198:370.e1–e7.
49. Hauge CR, Bonde PJ, Rasmussen A, Skovbjerg S. Mindfulness-based cognitive therapy for multiple chemical sensitivity: a study protocol for a randomized controlled trial. *Trials*. 2012;13:179.
50. Hooper A. Dynamic neural retraining system. http://www.dnrsystem.com/. Accessed October 18, 2011.
51. Boyd I, Rubin G, Wessely S. Taking refuge from modernity: 21st century hermits. *J Royal Soc Med*. 2012;105:523–529.
52. Genuis SJ. Elimination of persistent toxicants from the human body. *Hum Exp Toxicol*. 2011;30:3–18.
53. Genuis SJ, Birkholz D, Rodushkin I, Beesoon S. Blood, urine, and sweat (BUS) study: monitoring and elimination of bioaccumulated toxic elements. *Arch Environ Contam Toxicol*. 2011;61:344–357.
54. Katerndahl DA, Bell IR, Palmer RF, Miller CS. Chemical intolerance in primary care settings: prevalence, comorbidity, and outcomes. *Ann Fam Med*. 2012;10:357–365.
55. Sears M. The Medical Perspective on Environmental Sensitivities. Government of Canada: Canadian Human Rights Commission 2007. http://www.chrc-ccdp.ca/sites/default/files/envsensitivity_en.pdf. Accessed April 22, 2013.
56. Afram R. New diagnoses and the ADA: a case study of fibromyalgia and multiple chemical sensitivity. *Yale J Health Policy Law Ethics*. 2013;4: Article 4.

Address correspondence to: Stephen J. Genuis, MD, Faculty of Medicine, University of Alberta, 2935-66 Street, Edmonton, Alberta, Canada T6K 4C1. E-mail: sgenuis@ualberta.ca