

# 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 ac-

crued 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;xx:xxx) © 2013 Elsevier HS Journals, Inc. All rights reserved.

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

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*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 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 every-

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day 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,<sup>1,2</sup> and has become an increasing public health dilemma<sup>3</sup> in many jurisdictions throughout the globe.<sup>2,4-6</sup>

As is common with heretofore unexplained conditions, patients presenting with CS have been received unsympathetically by some medical practitioners.<sup>7</sup> 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<sup>8</sup> 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.<sup>9</sup> Major medical bodies such as the Centers for Disease Control and Prevention have established that many people in the population maintain a toxicant burden.<sup>10</sup> Considerable evidence has linked diverse health concerns to intense, acute exposure, as well as to repeated low-level exposure, to potentially toxic agents.<sup>9</sup> 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.<sup>11</sup> 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,<sup>12,13</sup> with major differences between exposed versus nonexposed employees within the same occupation.<sup>12</sup> Many articles discuss the initiation of sensitivity issues after contaminated air exposure within building settings.<sup>14-19</sup> Following the 9/11 disas-

ter 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.<sup>20-24</sup> 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.<sup>25</sup> In research settings, it is possible to induce sensitivity states in animals by exposing them to toxic insults.<sup>26-28</sup>

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<sup>29</sup> 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 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

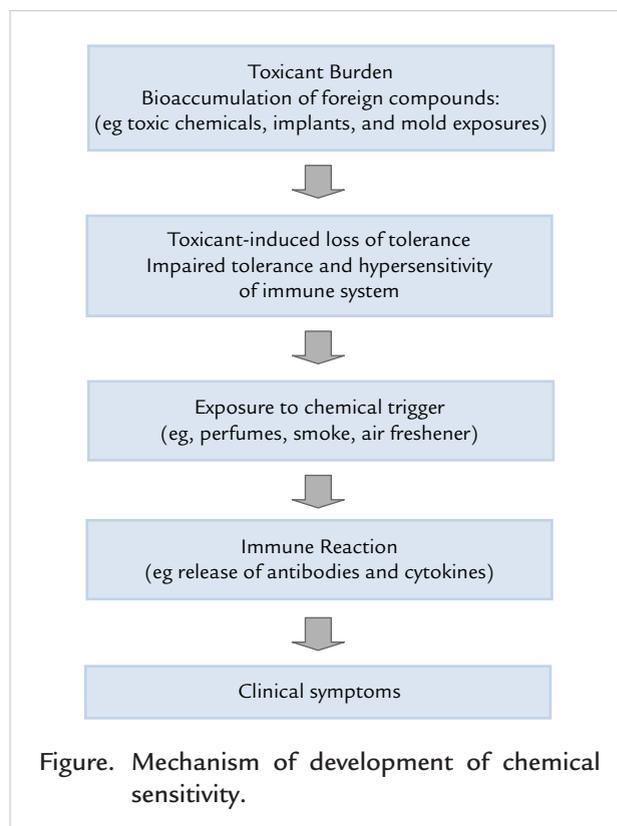


Figure. Mechanism of development of chemical sensitivity.

board-evoke diverse signs and symptoms,<sup>30,31</sup> 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<sup>32</sup> directly induce a sensitization effect on the immune system through induced dysregulation.<sup>33</sup> The consequent response to low-dose stimuli and resulting inflammation may be triggered by a reflex mechanism that initiates an inflammatory immune reaction,<sup>34</sup> 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.<sup>32,35</sup> Urban air particulate matter, for example, has been associated with a proinflammatory cytokine response in some individuals,<sup>36,37</sup> and bacterial contamination of indoor air has been found to stimulate cytokine release *in vivo*.<sup>35</sup> Inflammatory cytokines have been found in the nasal passages and lungs of individuals exposed to some toxicants,<sup>38,39</sup> 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.<sup>1</sup>

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.<sup>40</sup> 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.<sup>41,42</sup>

### 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),<sup>30,40</sup> 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.<sup>17,30</sup>

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).<sup>2</sup> 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.<sup>43,44</sup> 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. It can start at any stage of life as a direct consequence of adverse exposure but is eminently modifiable with appropriate therapeutic intervention.<sup>3,17,30,31</sup>

### Clinical Therapeutic Approach

Many therapies have been tried, with varying results, to address the problem of CS.<sup>45</sup> Symptomatic desensitization immunotherapies aimed at preempting the hypersensitivity immune response associated with exposure in susceptible individuals are being used.<sup>46</sup> 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.<sup>46–48</sup> 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,<sup>49,50</sup> but psychotherapeutic interventions have thus far not met with much reliable success.<sup>45</sup> Some patients choose to withdraw from society and become “21st century hermits” to avoid chemical triggers,<sup>51</sup> as 95% of CS respondents in 1 study claim that chemical avoidance and creating a chemical-free living space are consistently helpful.<sup>45</sup>

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.<sup>30</sup> The purging of the underlying toxicant burden through innate mechanisms of toxicant elimination or through clinical detoxification interventions for persistent pollutants<sup>52,53</sup> seems to consistently diminish the immune dysregulation associated with CS and to gradually ameliorate the clinical manifestations of CS.<sup>30</sup>

## 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.<sup>54</sup> 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,<sup>11</sup> 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,<sup>55</sup> and increasing dialogue regarding CS has been generated in the legal community.<sup>56</sup> As a preventable and reversible condition, CS requires public health attention to preclude toxicant exposures<sup>57</sup> and informed clinical care to alleviate the

suffering associated with CS and to preempt the potential chronicity of this disorder.

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## CONFLICTS OF INTEREST

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

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**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](mailto:sgenuis@ualberta.ca)