

## Chemical sensitivity: symptom, syndrome or mechanism for disease?<sup>1</sup>

Claudia S. Miller\*

*Department of Family Practice, Environmental Occupational Medicine, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78284-7794, USA*

---

### Abstract

Several different meanings have been attached to the term “chemical sensitivity” by those who use it. Feeling ill from odors is a *symptom* reported by approximately one-third of the population. The *syndrome* of chemical sensitivity, frequently called “Multiple Chemical Sensitivity” or “MCS” has been the subject of three federally-sponsored workshops; at least five different case definitions for research on MCS have been proposed. In contrast, the hypothesis that chemical sensitivity may be a *mechanism for disease* posits that a broad spectrum of “recognized” chronic illnesses, ranging from asthma and migraine to depression and chronic fatigue, may be the consequence of environmental chemical exposures. According to this theory, a two-step process occurs: (1) an initial salient exposure event(s) (for example, a one-time, intermittent, or continuous exposure to pesticides, solvents, or air contaminants in a sick building) interacts with a susceptible individual, causing loss of tolerance for everyday, low level chemical inhalants (car exhaust, fragrances, cleaning agents), as well as for foods, drugs, alcohol, and caffeine; (2) thereafter, such common, formerly well-tolerated substances trigger symptoms, thus perpetuating illness. “Masking” (acclimatization, apposition, and addiction) may hide these exposure-symptom relationships, thus obfuscating the environmental etiology of the illness. Accumulating clinical observations lend credence to a view of chemical sensitivity as an emerging theory of disease causation and underscore the need for its testing in a rational, scientific manner. While chemical sensitivity may be the consequence of chemical exposure, the term “toxicant-induced loss of tolerance” more fully describes the two-step process under scrutiny.

**Keywords:** Chemical sensitivity; Theory for disease; Environmental exposure; Environmental etiology; Toxicant-induced loss of tolerance

---

\*Corresponding author, Tel.: 210-567-4577; Fax: 210-567-4579.

<sup>1</sup>Presented in part at the Tri-Service Toxicology, US Environmental Protection Agency, and Agency for Toxic Substances and Disease Registry Interagency Conference on Risk Assessment Issues for Sensitive Human Populations, Wright-Patterson Air Force Base, Ohio, April 25–27, 1995.

### 1. Introduction

The Eskimos have many words in their language for “snow” — there is freshly fallen snow, snow with an icy crust on it that crunches underfoot, fine snow, snow that drifts, snow that clings, soft, deep snow, and so on (Woodbury, 1991).

Snow is an integral part of Eskimo life. In the United States, there are now more than a dozen names for chemical sensitivity: some of these names imply a particular cause (e.g. the petrochemical problem, chemophobia), some describe the effect (e.g. universal allergy, multiple chemical sensitivity), and others insinuate a particular mechanism (e.g. immune dysregulation, odor conditioning) (Ashford and Miller, 1991). "Chemical sensitivity" and "multiple chemical sensitivity" ("MCS") appear favored at present. These terms describe the most distinctive feature of the illness without presuming a particular etiology or mechanism. Notably, some feel that even "MCS" is too much of a legitimizing label and have suggested that "multiple symptom complex" might be less objectionable (Gots et al., 1993).

Some physicians and researchers believe that MCS is a psychogenic phenomenon which most closely resembles depression, somatoform disorder or post-traumatic stress disorder. Others think that MCS is caused by chemical exposures and, further, that chemical sensitivity may underlie a host of "recognized" chronic illnesses, including asthma, migraine headaches, depression, fibromyalgia, and chronic fatigue syndrome. Still others remain agnostic, awaiting more evidence before proffering opinions.

Authors of scientific articles have used the term "chemical sensitivity" in different ways and in different contexts to "mean just what they choose it to mean" (Humpty Dumpty, Lewis Carroll). Words have consequences and a shared understanding of the term "chemical sensitivity" is essential if Jabberwockian *nonscience* (read: nonsense) is to be avoided. The purpose of this paper is to explore the meanings that have been imputed to the term "chemical sensitivity," and, by the close of this paper, convince the reader of the seriousness of the current confusion over its meaning, and how more precise terminology could lead to clearer thinking and greater understanding in this area. Risk assessment, the focus of this conference, requires that we "count the bodies" of those who are afflicted. How we define chemical sensitivity greatly affects this count.

The history and phenomenology of chemical sensitivity, as well as the panoply of hypotheses

that have been advanced to explain it are discussed in detail elsewhere. In the past eight years, two reports sponsored by state agencies (Ashford and Miller, 1989; Bascom, 1989), two books written for occupational health professionals and researchers (Cullen, 1987; Ashford and Miller, 1991), and the proceedings of three federally-sponsored meetings that focused on chemical sensitivity (Association of Occupational and Environmental Clinics, 1992; National Research Council, 1992; Agency for Toxic Substances and Disease Registry, 1994) have been published. A review of these and other recent publications on MCS reveals that the term "chemical sensitivity" is most often used in one of three contexts: (1) to describe a symptom; (2) to serve as a kind of shorthand for an allegedly new medical phenomenon or syndrome; and (3) to characterize what some view as an emerging mechanism for disease. Depending upon which of these contexts is meant, the number and types of persons who might be chemically sensitive varies greatly, and there are enormously different consequences for patients, industry, policymakers and risk assessors. In the next sections, we will explore each of these contexts and the consequences which flow from them.

## 2. Chemical sensitivity: the symptom

The simplest and perhaps least judgmental application of the term "chemical sensitivity" has been its use to describe the symptom of feeling ill from chemical odors. While the word "cacosmia" has been used in the occupational health literature to describe this symptom, neither this term nor the word "dysosmia" fully convey the observation that MCS patients *feel ill* when they confront certain odors. An alternate term that would convey this might be "pathosmia." Illness from odors has been reported in 60% of a group of solvent-exposed workers (Ryan et al., 1988; Morrow et al., 1990). It also has been reported among agricultural workers following acute organophosphate intoxication (Tabershaw and Cooper, 1966) and among workers in chemical warfare agent production facilities (SIPRI, 1975).

Table 1  
Frequency of chemical/odor sensitivity in selected populations

Population	n	Question posed	% Answering affirmatively
EPA office workers (EPA, 1989)	3955	Do you consider yourself especially sensitive to ... (various indoor air contaminants)?	31%
Arizona* elderly living in planned retirement community (Bell et al., 1994)	192	Do you consider yourself especially sensitive to certain chemicals?	34%
University of Arizona* college students in introductory psychology class (Bell et al., 1995)	809	Do you consider yourself especially sensitive to certain chemicals	28%
Rural North Carolinians (Meggs et al., 1994)	1027	Some people get sick after smelling chemical odors like those of perfume, pesticides, fresh paint, cigarette smoke, new carpet, or car exhaust. Other people don't get sick after smelling odors like these. Do any chemical odors make you sick?	33% (39% of women; 24% of men)

\*A haven for pollen-allergy sufferers in the past, Arizona is thought to have the highest percentage of atopic individuals of any state.

How prevalent is the *symptom* of chemical sensitivity, or pathosmia? To date, no randomized, population-based survey that would answer this question for the nation as a whole has been conducted. However, several smaller surveys suggest that 28–34% or approximately one-third of the population considers itself especially sensitive to certain odors (Table 1). Notably, most of the participants in these surveys who reported that certain odors made them feel ill were neither sick nor disabled. Thus, while approximately one in three Americans reports that certain odors cause illness, the majority of these individuals differ substantially from MCS patients. Whether with sufficient exposure any, some, most, or all of these individuals might develop MCS remains to be determined. Nevertheless, it seems fair to say that the symptom of feeling ill from chemical odors is not identical to nor specific for MCS.

Thus chemical sensitivity—the symptom—lacks specificity for the condition under scrutiny. It may also lack sensitivity. That is, individuals who may be chemically sensitive may not be aware that they are chemically sensitive (for example, migraineurs, chronic fatigue sufferers). “Masking” (to be discussed in a later section) may interfere with this awareness. Thus, the

symptom of chemical sensitivity or pathosmia, while prevalent in the general population, is not very specific, and, indeed, also may be insensitive as an indicator of illness associated with low level chemical exposures. Notwithstanding, the term “pathosmia” has value for descriptive clinical and research purposes. Its adoption for describing the symptom of feeling ill from chemical odors may be preferable to the term “chemical sensitivity” which has acquired other meanings, as shall be discussed.

### 3. Chemical sensitivity: the syndrome

A “syndrome” is “a *group* of symptoms or signs typical of a disease” (Webster’s, 1986). Many have objected to labelling chemical sensitivity a syndrome because the patients report such diverse symptoms. Indeed, while individual patients report that their symptoms occur reproducibly following exposure to specific substances, unlike other recognized syndromes there is no archetypical constellation of symptoms that constitutes MCS. This fact has thwarted development of a case definition for the illness. While a precise MCS case definition would be desirable for research purposes, restricting thinking about

chemical sensitivity to any immutable set of symptoms or number of organ systems could prematurely constrict the field of view. For example, some proposed MCS case definitions exclude asthma or depression on the grounds that these are “diagnosable” conditions. Yet asthma or depression might themselves be the consequence of low level chemical exposure. In contrast, *exposure (or event) driven studies*, for example studies of office workers in a sick building or residents of a community exposed to a toxic spill, could yield a fuller understanding of the range and nature of illnesses that ensue (National Research Council, 1992). More specifically, it is conceivable that exposure to emissions from new carpeting in a poorly ventilated office building could cause or exacerbate a panoply of conditions, with the occupants’ personal (genetic, nutritional, etc.) vulnerabilities determining which specific symptoms manifest in any individual case. Indeed, some researchers have suggested that RADS (Reactive Airways Dysfunction Syndrome), an asthma-like condition that develops after an acute chemical exposure and leaves its sufferers sensitive to chemically-diverse inhalants, may be a pulmonary manifestation of MCS (Meggs and Cleveland, 1993). Still others hypothesize that certain cases of depression and somatoform disorder may be caused or exacerbated by chemical exposures and thus could share the same biochemical underpinnings as MCS (Rosenthal and Cameron, 1991; Bell, 1994). Then there are odor-triggered migraines and seizures. Might these be induced by the same mechanisms that underlie MCS? Limiting the search for chemical sensitivity to any predetermined set of symptoms or clinical criteria makes little sense when we are in such an early observational stage in this illness.

At least five case definitions for research on chemical sensitivity have been published (summarized in Miller, 1994), yet consensus on a single definition has not emerged, again largely because of the heterogeneity of symptoms patients report. Miller and Mitzel (1995) compared two groups of MCS patients—37 who attributed onset of their illness to a well-defined exposure to a cholinesterase-inhibiting pesticide and 75 who

attributed onset of their condition to remodeling of a building. Despite differences in *individual* symptom patterns and different initial exposures, the two *groups* exhibited strikingly similar frequencies and ordering of symptoms. The authors interpreted these findings as suggesting a shared mechanism or final common pathway leading to the same disorder in both groups.

Some view the fact that no symptom-based case definition for MCS has achieved broad acceptance as evidence that the condition does not exist. On the other hand, this lack of consensus could be a serendipitous clue that chemical sensitivity is not a *single* syndrome, but a *collection* of syndromes that share the same general mechanism, much as cholera, influenza and Rocky Mountain Spotted Fever share the same general mechanism, in this case, infectious transmission.

#### 4. Chemical sensitivity: a mechanism for disease?

The Civil War marked the last major armed conflict fought in the world without knowledge of microbes or infectious disease (Sartin, 1993). A few years later, Pasteur, Lister, Koch and others made their discoveries which led to the germ theory of disease. Two-thirds of the approximately 660 000 deaths among soldiers during the Civil War were caused by infections, most frequently wound infections and epidemics. Diagnoses were based on clinical signs. Fever cases were divided into three categories: remittent, intermittent, and relapsing. Cases assigned to those categories likely included typhus, typhoid, malaria, abscesses, tuberculosis, leptospirosis, borrelia, pneumonia, influenza, infectious diarrheas and others. Brucellosis, tularemia, leptospirosis and Q fever likely were present too, but put in other categories such as “miasmatic diseases, unclassified.” Civil War surgeons commonly attributed diseases to toxic miasma or “effluvia” from the wet swamplands of the South where many battles were fought or to inadequate ventilation in the tents (Sartin, 1993).

It is possible that we may be at the Civil War stage in our understanding of chemical sensitivity. Chemical sensitivity could be an emerging mechanism or theory of disease, one that en-

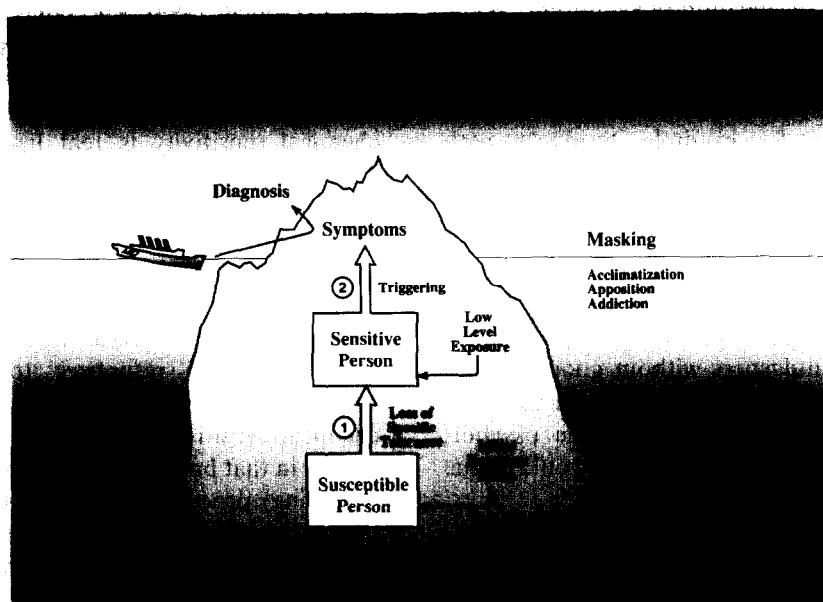


Fig. 1. Phenomenology of chemical sensitivity. Chemical sensitivity appears to develop in two stages: (1) loss of specific tolerance following acute or chronic exposure to various environmental agents, such as pesticides, solvents or contaminated air in a sick building, and (2) subsequent triggering of symptoms by extremely small quantities of previously tolerated chemicals, drugs, foods, and food/drug combinations (e.g. traffic exhaust, fragrances, caffeine, alcohol). Physicians formulate a diagnosis based upon symptoms reported to them by their patients. Because of masking, both physicians and patients may fail to "see" that everyday, low-level exposures may be triggering symptoms. Even when such triggers are recognized, an initial exposure event which may have initiated loss of specific tolerance may go unnoticed or may not be linked to the patient's illness.

compasses a wide range of chemical agents acting on different organ systems via different specific mechanisms, just as the category "infectious diseases" subsumes a wide range of vectors affecting different organ systems via different specific mechanisms resulting in heterogeneous symptoms. Is there any evidence to support such a notion?

If chemical sensitivity were a candidate for a theory of causation for disease, at the very least it would need to embrace MCS, the most prototypical of the chemical sensitivity "diseases," and would need to account for the clinical observations associated with MCS. These observations are discussed in detail elsewhere (Ashford and Miller, 1989, 1991; Miller, 1994) and summarized in Fig. 1. Briefly, chemical sensitivity appears to entail two steps: (1) induction, and (2) triggering. The inducing or initiating exposure may involve any of a wide variety of substances, including

pesticides, solvents, indoor air contaminants, drugs, etc. It may be acute as in a chemical spill, intermittent as in many industrial exposures, or chronic as in a sick building. *Loss of tolerance* appears to occur as a consequence of this initial exposure. Subsequently, extremely low levels of chemicals, levels that do not bother most people and were never a problem for that individual before, trigger symptoms. In addition, alcoholic beverages, caffeine, nicotine, various foods and drugs may trigger symptoms. On the surface, "loss of tolerance" may sound like a vague and ill-defined concept, the product of arm-chair theorizing. Clinically, it is neither vague nor ill-defined. What MCS patients describe is a loss of tolerance for *specific* inhalants, drugs, foods, etc. This loss of tolerance is reported to spread to an increasing number of substances as the problem progresses. When MCS patients are re-exposed to these specific substances, they say they experi-

ence a discrete constellation of symptoms. While the symptoms that are triggered by a given agent are highly individual, they are reportedly reproducible for a particular patient following a particular exposure, for example, headache with diesel exhaust, mental confusion with a certain fragrance, nausea with cashews, and so on. Notably, many MCS patients and Gulf veterans now forego chocolate, favorite foods like pizza, or alcoholic drinks because they say these make them so sick (Miller, 1994). Most of us would not give up these indulgences without good cause—there seems little secondary gain to be garnered from such abstinence, although some psychologists and psychiatrists, no doubt, would argue otherwise.

Thus, loss of specific tolerance is a focused, well-defined construct, one no more fuzzy than the General Adaptation Syndrome and its associated concepts of stress and stressors were when Hans Selye first introduced them.

Chemical sensitivity has been accused of contradicting the fundamental principles of toxicol-

ogy (Waddell, 1993). The same might have been said for allergy (or even cancer) when it was first discovered, and is even true now. Allergy's rules differ greatly from those of toxicology, and, if chemical sensitivity is real insofar as being a disease mechanism, it seems to follow still another set of rules. Chemical sensitivity appears to have major overlaps with toxicity, allergy and addiction (Table 2), yet it does not adhere to all of the rules for any one of these.

Like toxicity, chemical sensitivity appears to involve adverse responses to environmental chemical contaminants, yet, mechanistically, chemical sensitivity more closely approximates allergy in that both involve a two-step (induction, triggering) process and subsequent "hypersensitivity." As with addiction, patients with chemical sensitivity report stimulatory and withdrawal symptoms. Unlike addiction, these responses occur not only to drugs, but also apparently to combustion products, fragrances, solvents and even foods. However, instead of manifesting addicted behaviors (*L. ad* "toward" + *dicare* "pro-

Table 2  
Features of chemical sensitivity that overlap addiction, allergy, and toxicity

Feature	Chemical sensitivity <sup>a</sup>	Addiction <sup>a</sup>	Allergy <sup>a</sup>	Toxicity <sup>a</sup>
Chemical/drug intolerances	+	+	+	+
Ambient air incitants	+		+	+
Food intolerances	+		+	
Alcohol intolerance	+	+		
Caffeine intolerance	+	+		
Withdrawal symptoms	+	+		
Craving, bingeing	+ (foods)	+ (drugs)		
Sensitization	+		+	
Induction by chemicals	+		+	+
Induction by biologicals			+	
Multi-system symptoms	+	+	+	+
Frequent CNS symptomatology	+	+		+
Well-defined mechanism(s)			+	+
Genetic susceptibility	+	+	+	+
Dose/response relationship	+ <sup>b</sup>		+ <sup>b</sup>	+

<sup>a</sup>Categories are not "pure" and may overlap in a given host, e.g. haptentation of a chemical toxin may initiate an immunologic response; brain and liver toxicity may accompany alcohol addiction.

<sup>b</sup>Dose-response does occur for allergens: with the first, sensitizing exposure for a susceptible individual, there is a dose-response relationship; with subsequent exposures, the sensitized person also responds in proportion to dose, but at a much lower dose level (Waddell, 1993). The same kind of dose-response relationship may pertain for chemical sensitivity, but has not been tested. However, individuals with MCS report increasingly severe symptoms the longer they remain in an exposure situation, an observation which hints at a dose-response interaction.

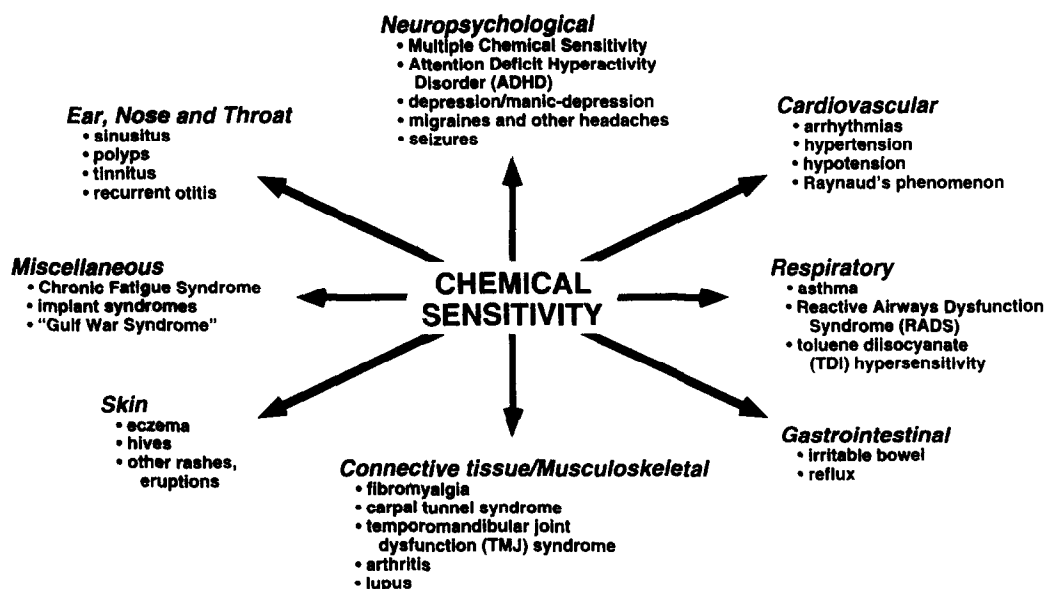


Fig. 2. Conditions that have been attributed to chemical sensitivity. (Of course, illnesses like depression, migraine, arthritis, hives, etc. may have many different etiologies. At most, chemical sensitivity might explain only a subset of these conditions. The question is, for each illness, how large is that subset and how might physicians distinguish those cases from similar cases with different etiologies).

claim”), patients act as though they are *ab*-dicted (*L. ab* “away from” + *dicare* “proclaim”) and assiduously *avoid* the very substances addicted individuals frequently favor, for example, alcohol, drugs, nicotine, and caffeine.

A major criticism of chemical sensitivity is that it has been claimed as a basis for “literally any physical or mental illness” (Waddell, 1993). Indeed, the range of illnesses that have been attributed to chemical sensitivity is enormous (Fig. 2) and involves any and all organ systems. Notably, and perhaps analogously, infectious diseases and immunological conditions also can affect virtually any organ system, so this criticism does not in any way negate the possibility that chemical sensitivity exists. In fact, close inspection reveals intriguing parallels between chemical sensitivity and the germ and immune theories of disease (Table 3). Each of these three theories embraces a wide range of specific agents or exposures. Included under each of these three categories are heterogeneous specific mechanisms (for example, the mechanisms of viruses vs. bac-

teria vs. rickettsia, or immediate vs. delayed-type hypersensitivity). Nonetheless, these diverse mechanisms still fall within the same general category, that is, infectious diseases or immunological diseases. Each of the three categories contains specific named syndromes or diseases. And each category contains processes that can affect literally any organ system. The specific manifestations of a given disease process in each of these categories depend on the nature of the original incitant and the vulnerabilities of the host, whether the category is infectious diseases, immunological diseases or chemical sensitivity. *Between* categories, symptoms are quite similar—malaise, rashes, headaches, shortness of breath, and diarrhea are common, non-specific manifestations for many illnesses. There is nothing pathognomonic about such symptoms. They can accompany an infectious process just as readily as an immunological or toxic one. It is the specific syndromes or named diseases within categories that have recognizable constellations of symptoms which facilitate diagnosis. Thus, rather

Table 3

Comparison of key features of three theories of disease: the germ theory, immune theory and chemical sensitivity theory

Disease theory	Explanation for disease	Symptoms	Particular diseases/syndromes	Agents	Exposure routes	Organ systems affected
Germ (Infectious)	Biological agent or "germ" multiplies in host (infection); germs can be transmitted to other organisms	Fatigue, malaise, fever, rash, headache, nausea, vomiting, diarrhea, shortness of breath, shock	Malaria, influenza, chicken pox, cholera, Lyme disease, AIDS, pneumonia	Bacteria, viruses, parasites, fungi, rickettsia	Inhalation, ingestion, injection, skin/mucous membrane contact	Any organ system or several at once
Immune	Host responds to foreign substance (antigen) by producing antibodies which "remember" the antigen and help ward it off in the future	Malaise, rash, pruritus, rhinorrhea, wheezing, shortness of breath, diarrhea, fever, laryngeal edema, shock	Allergic asthma, hives, poison ivy, penicillin allergy, peanut allergy	Pollen, mold, house dust mite, animal dander, foods, biologicals (drugs)	Inhalation, ingestion, injection, skin/mucous membrane contact	Any organ system or several at once
Chemical Sensitivity	Environmental exposure causes loss of specific tolerance in host, who subsequently develops symptoms when exposed to low levels of chemically diverse substances	Fatigue, malaise, memory difficulties, depression, irritability, headaches, digestive problems, shortness of breath, odor intolerance	Multiple chemical sensitivity, "Gulf War Syndrome" (?), chronic fatigue syndrome (?), post-implant syndromes (?), reactive airways dysfunction syndrome (RADS)	Solvents, pesticides, combustion products, drugs, implants	Inhalation, ingestion, injection, skin/mucous membrane contact	Any organ system or several at once

than being a syndrome *per se*, chemical sensitivity has many of the earmarks of an emerging category of disease. Such an unproven, yet-to-be-tested general mechanism for a collection of illnesses is a *theory of disease*.

Recalling the critics view that chemical sensitivity is not a syndrome because no definable set of symptoms is associated with it, the critics make an important point: chemical sensitivity may no more be a syndrome than infectious diseases and immunological diseases are syndromes. Nor is there any conceivable case definition that would cover all infectious diseases or all immunological diseases. Case definitions simply have limited utility when we are discussing categories of disease.

Could chemical sensitivity be an emerging new theory of disease? In 1868, while commenting on the usefulness of the germ theory of disease, Max Boehr provided a remarkably insightful and concise synopsis of the criteria for choosing among alternative theories (Carter, 1985). He noted that "the theory of infection has the characteristic of all good pathological and physiological theories; it provides a unified, clear, and entirely intelligible meaning for a whole series of anatomical and clinical facts and for the relevant experiences and discoveries of reliable observers during epidemics." Likewise, chemical sensitivity is a theory of disease that could unite disparate clinical observations and that may enable practitioners to predict patient responses under conditions of

Table 4  
Frequency of selected symptoms reported as severe<sup>a</sup> by Gulf veterans, MCS patients and controls

Symptom	Gulf veterans (n = 59)	MCS pesticide-exposed (n = 37)	MCS remodeling-exposed (n = 75)	Controls <sup>b</sup> (n = 112)
Fatigue	78%	68%	52%	3%
Depression	29	49	33	6
Headaches	53	38	31	5
Shortness of breath	38	43	31	2
Asthma or wheezing	12	27	15	0

<sup>a</sup>Participants rated their symptoms on a 0–3 scale: 0, not at all a problem; 1, mild; 2, moderate; 3, severe. Frequencies listed in this table reflect ratings of severe (3) only.

<sup>b</sup>Age, sex and education-matched to the two MCS groups (37 + 75 = 112).

exposure and avoidance. While clinical observations on MCS accumulated to date do not constitute proof of the condition's existence, they are hypothesis-generating and provide the foundation for what could be an emerging theory of disease, a theory worthy of careful scientific testing.

Some have proposed that the same mechanisms that are operative in chemical sensitivity might underlie conditions like fatigue, depression, headaches and asthma. If one compares the frequency of these particular conditions among groups of ill Gulf veterans and MCS patients to the frequency of these same conditions among controls (matched for age, sex and education to the MCS patients), 5 to 15 times as many Gulf veterans and MCS patients report *severe* fatigue, depression, headaches, shortness of breath, asthma or wheezing as controls (Table 4). Thus, Gulf veterans and MCS patients who attribute their illness to an "exposure event" represent an enriched sample of the population for these conditions. This finding suggests that at least a subset of persons suffering from headaches, chronic fatigue, asthma or depression might be chemically sensitive. It is noteworthy that persons with these conditions often share the same exposures and environments that MCS patients say caused their illness.

Anomalies often pave the way for discovery. The anomalous observation that individuals who survived a particular infection rarely contracted that infection again led to the immunologic con-

cept of disease. The anomaly of MCS could likewise expand our thinking about disease causation. Thomas Kuhn (1970) observed that theories are "generally preceded by a period of pronounced professional insecurity. As one might expect, that insecurity is generated by the persistent failure of the puzzles of normal science to come out as they should. Failure of existing rules is the prelude to a search for new ones." Perhaps, we are in what Kuhn characterizes as a pre-paradigm period, a time "regularly marked by frequent and deep debates over legitimate methods, problems, and standards of solution, though these serve rather to define schools than to produce agreement."

## 5. Masking

If individuals with migraines, chronic fatigue, asthma or depression were suffering from chemical sensitivity, why wouldn't more of them report specific chemical intolerances just like MCS patients do? In fact, many MCS patients say that when they first became ill, they had no idea chemical exposures had anything to do with their symptoms. They say it was not until they avoided (accidentally or intentionally) a sufficient number of their problem incitants simultaneously that they noticed feeling better. Then, when they re-encountered something to which they were sensitive, their symptoms recurred. Thus, MCS patients claim that only through the tandem process of avoidance and re-exposure were they able to

learn which exposures triggered their symptoms. Had they not systematically avoided a wide range of exposures first, or "unmasked" themselves, accidentally or intentionally, most say they would not have figured out what was making them sick. This lay term, "masking," sounds deceptively simple. In fact, what patients mean by masking is technically quite complex. Understanding masking may be fundamental to understanding chemical sensitivity, its potential role in chronic illness and how such a theory of disease might be tested scientifically. When MCS patients talk about "unmasking," they are describing a complex phenomenon that is poorly understood but experientially recognizable to most of us. There are at least three components involved in masking: acclimatization, apposition and addiction (Fig. 3). "Unmasking," that is, avoiding multiple potential incitants simultaneously, overcomes each of these three components of masking.

The most rigorous approach to unmasking, an approach developed in the 1950s by allergist Theron Randolph, involves placing an individual in an environmentally-controlled hospital unit (not an exposure chamber) and restricting food and drug intake for several days to a week. This approach (described in Ashford and Miller, 1991), eliminates any *acclimatization* that may have developed in a sensitive individual as a consequence of chronic or repeated exposure to an incitant, for example, indoor air contaminants in a sick building. It simultaneously allows the avoidance of inhalation, ingestion and dermal contact for most chemicals, foods, and drugs, thus preventing overlapping symptoms that might occur in a sensitive individual experiencing multiple, overlapping exposures (*apposition*). Finally, this approach interrupts any *addiction* due to repeated exposure to caffeine, alcohol, nicotine or other addictive substances. Fig. 3 depicts each of the components of masking. In effect, masking and unmasking pertain to the *state* of the patient—the underlying illness remains constant. Depending on background environmental conditions, chemical sensitivity seems to occur in masked and unmasked varieties which outwardly appear different but are intrinsically the same.

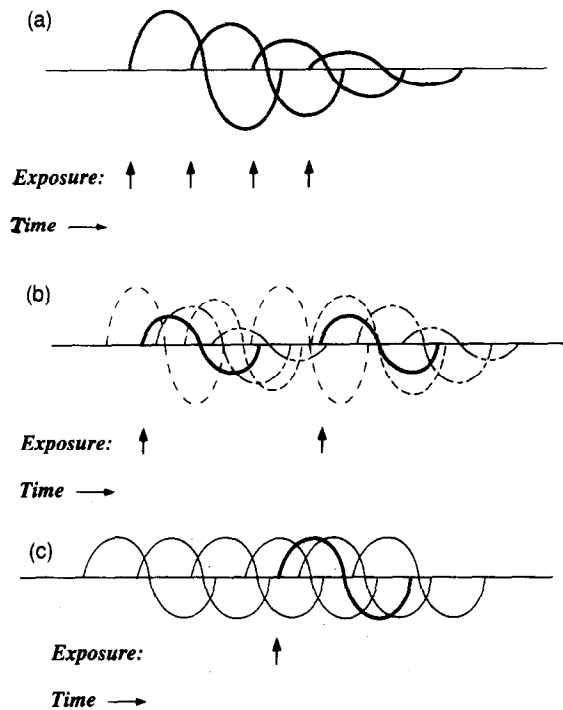


Fig. 3. Components of masking. Each biphasic curve is a graphical representation of symptoms occurring in a sensitive individual with onset and offset of a particular exposure. For solvents, caffeine, alcohol, nicotine, etc., the portion above the line represents stimulatory symptoms and the portion below withdrawal symptoms. Amplitude is proportional to symptom severity. For a person who is not particularly sensitive to the substance, the curves would be flat or nearly flat. Solid curves represent the effect of interest, that is, a response to a particular chemical or food one is trying to observe during a challenge with that substance. (A) Acclimatization: symptom severity decreases with repeated, closely-timed exposures to the same substance. Although seemingly paradoxical, sensitivity may increase during acclimatization. In real life, time intervals between exposure may vary greatly, so that a person may be acclimatized to varying degrees at different times, and thus, from day to day, experience varying intensity of symptoms. However, the most robust effect of a challenge would be expected in the sensitive individual who is not acclimatized. (B) Apposition: if an individual is sensitive to many different substances, then the effects of everyday exposures to chemicals, foods or drugs may overlap in time. This apposition of effects might yield an individual who feels bad most of the time, but the effect of any single exposure is not apparent either to the individual or his physician. Apposition would tend to mask the effect of interest in much the same way that background noise masks a sound of interest. (C) Addiction: a sensitive person who is addicted to caffeine, alcohol, nicotine, or other substances may deliberately take the substance at frequent, carefully-spaced intervals to avoid unpleasant withdrawal symptoms. Such exposures may also mask an effect of interest.

There are no scientific equivalents for the terms “masking” or “unmasking.” “Adaptation” and “de-adaptation” (terms previously used by this author) have other connotations that seem to confuse rather than clarify understanding of this concept; inevitably their use leads to a discussion as to whether adaptation or pseudoadaptation is occurring (for example, in cigarette smokers who develop apparent tolerance for the irritative properties of tobacco smoke, but may experience long-term deleterious consequences from tobacco use). Understanding masking may be crucial to understanding chemical sensitivity. As long as patients with depression, migraines, fatigue, etc. are masked, it may be impossible to tell whether there is any relationship between their symptoms and low level environmental exposures. They must first be unmasked. Testing such patients in a masked state would be like trying to find out whether headaches in a coffee drinker with a 10–15 cup per day habit were due to caffeine by giving him a cup of coffee and asking how it made him feel. It is intuitively obvious that the individual would need to stop using all or most caffeine (unmask him for caffeine) before a meaningful test of caffeine sensitivity could be performed. Falsely negative challenges are likely to result from failure to unmask. This experimental requirement of unmasking brings to mind the enormous difficulty researchers encountered during the late nineteenth century in trying to isolate the organism responsible for tuberculosis. Many researchers collected fluids from TB patients but were unsuccessful in culturing any organism. At the time, these researchers were unaware that the organism was extremely fastidious and would only grow out after weeks on a specialized culture medium. Some who failed to grow the organism concluded that TB was not an infectious disease at all. Correspondingly, our ability to “see” chemical sensitivities may rest upon optimizing experimental conditions, i.e. using the appropriate culture medium, in this case an environmental unit for unmasking and studying this phenomenon. Absent such an approach, erroneous conclusions about the existence of MCS may be reached as a consequence of inadequately

designed experiments resulting in falsely negative data.

#### **6. Testing the theory of chemical sensitivity: the need for postulates**

Following the introduction of the germ theory of disease in the late 1800s, many overly enthusiastic researchers employing careless bacteriological technique claimed to have discovered the causative agents for diseases such as TB or Yellow Fever. So frequent were these pronouncements and subsequent retractions that in 1884 the President of the New York Academy of Medicine, Abraham Jacobi, “lamented the ‘bacteriomania’ that had swept the medical profession” (Warner, 1985). In order to preclude further such pseudodiscoveries, Koch, who identified the organisms that cause tuberculosis, anthrax and cholera, suggested adoption of a set of rules for etiological verification, now known as Koch’s postulates:

- (1) The microbe must be present in every case of the disease.
- (2) It must be isolatable in pure culture.
- (3) Inoculating a healthy animal with the culture must reproduce the disease.
- (4) The microbe must be able to be recovered from the inoculated animal and grown again.

In comparable fashion, research on chemical sensitivity today is in need of a set of scientific principles or postulates that will ensure that causal determinations in this area are scientifically based. Fig. 4 illustrates use of an environmental medical unit as a means of testing responses to low level environmental exposures, and depicts four postulates which, if met, would establish proof of a cause-and-effect relationship between symptoms and a particular exposure or incitant, if such a relationship exists. These postulates are:

- (1) When the sensitive individual simultaneously avoids all chemical, food, and drug incitants, remission of symptoms occurs.
- (2) Symptoms occur with reintroduction of an incitant.
- (3) Symptoms resolve when the incitant is again avoided.

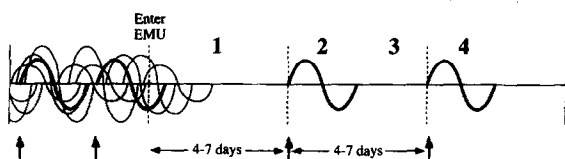


Fig. 4. Graphical representation of chemical sensitivity postulates. In the left-most portion of the figure, before entering an environmental medical unit (EMU), a chemically sensitive individual is experiencing symptoms in response to multiple exposures (chemicals, foods, drugs). Effects overlap in time. The effect of any particular exposure does not stand out from those of other exposures and the person's symptoms appear to wax and wane unpredictably over time. Postulate 1: when all chemical, food and drug incitants are concurrently avoided, remission of symptoms occurs. Postulate 2: symptoms occur with reintroduction of an incitant. Postulate 3: symptoms resolve when the incitant is again avoided. Postulate 4: re-exposure to the same incitant, within an appropriate window of time (estimated to be about 4–7 days), produces the same symptoms. For research purposes, challenges should be conducted in a double-blind, placebo-controlled manner.

(4) With re-exposure to the same incitant, the same symptoms recur, provided that the challenge is conducted within an appropriate window of time (ideally 4–7 days after the last exposure to the incitant).

Note that for research purposes, challenges of this type should be performed in a double-blind, placebo-controlled manner (Ashford and Miller, 1991). This approach could be extended to patients with MCS, chronic fatigue, migraines, seizures, depression, asthma, and other conditions to determine whether or not a particular person's illness is a *forme masquée* of chemical sensitivity.

What evidence is there that unmasking patients in an environmental unit and adhering to a 4–7 day window of time between challenges are important for this process? Only the observations of thousands of credible patients and dozens of physicians who have attempted this maneuver. Physicians and patients who have followed this procedure report impressively robust symptoms following food and chemical challenges. Given that clinical observations are the wellspring of most new medical ideas, we must guard against dismissing these patients' reports without trying

first to recreate the circumstances in which they say their responses are most clearly elicited. Some researchers may argue that an environmental unit and unmasking should not be necessary if patients are experiencing symptoms with daily exposure. It is true that an effect may be seen with exposure challenges outside of a unit. However, certain problems can be anticipated. First, patients' responses will not be as robust if unmasking and appropriate timing between challenges are not considered. But, more concerning, patients' responses may not be reproducible from one day to the next. For example, if patients must drive through heavy traffic to get to an exposure chamber in order to undergo a challenge, their responses to the challenge may be blunted or perhaps disappear entirely. Conversely, if a *placebo* is administered, sensitive individuals might still be experiencing delayed effects of their exposure to car exhaust while in transit to the laboratory, and falsely positive responses could occur.

## 7. Chemical sensitivity: the need for new terminology

Applying the moniker "chemical sensitivity" to the theory of disease described above fails to convey adequately either the potentially disabling nature of the condition or its induction by an earlier exposure event. The two-step process that has been described for chemical sensitivity begins with a chemical exposure which appears to be "toxic," that is, it causes adverse effects in at least a subset of individuals (i.e., when they subsequently are exposed to different substances). These individuals report life- and career-disrupting disability following an identifiable initial exposure. While Paracelsus aptly stated that dose makes the poison, in truth, "dose + host" makes the poison (for example, pack-years of tobacco smoked + the  $\alpha$ -1-antitrypsin-deficient individual). Admittedly, the nature of the initial "toxicity" in chemical sensitivity departs radically from that of classical toxicity (Table 2). Clinically, this "toxicity" more closely resembles allergic sensitization, although, here again, there are major differences, which include the exquisite specificity of

antibodies for antigens versus the spreading of sensitivities to structurally unrelated chemicals that is reported by chemically sensitive patients.

In effect, chemical sensitivity is a sort of “cryptotoxicity.” “*Crypto*” (Gk. “hidden”) because of:

(1) The frequently hidden or imperceptible nature of the initial exposure(s) that causes loss of specific tolerance. This event may go unnoticed entirely or may not be connected causally with onset of illness by patient or physician. For example, an illness that develops following routine household extermination or administration of a general anesthetic may be attributed to some other cause. If several residents of a home recently treated with pesticides develop flu-like symptoms at the same time, an infectious cause may be assumed erroneously.

(2) The diversity of clinical presentations that occur, even among those who share the same inducing exposure event(s) (e.g. identically or near-identically exposed family members or co-workers). Such symptom heterogeneity in an exposed group would tend to “hide” the presence of a discrete illness, thus thwarting standard epidemiological approaches to investigating an outbreak.

(3) Masking via acclimatization, apposition and addiction, which have been described previously. Following loss of specific tolerance, masking obfuscates the relationship between symptoms and triggering exposures.

The term “toxicant-induced loss of tolerance” (acronym “TILT”) might describe this cryptotoxic theory of disease more parsimoniously. An analogy comes to mind here: with a pinball machine, a player has just so much latitude—he can jiggle the machine, nudge it, bump it, rock it, but when he exceeds the limit for that machine, the “TILT” message appears, the lights go out, and the ball cascades to the bottom. The machine’s tolerance has been exceeded and no amount of effort will make the bumpers or flippers operate as they did before. The game is over. A colleague recently suggested that another reason a pinball analogy was apt was the fact so many MCS patients bounce around from one specialist to another. Indeed the average MCS

patient in one study had consulted nearly ten physicians (Miller and Mitzel, 1995).

Is *another* name for chemical sensitivity really necessary? Notably, the term “allergy” might have sufficed. Patients with chemical sensitivities spontaneously refer to their responses as “allergies.” Indeed, when Von Pirquet coined the word “allergy” in 1906, he defined it as “altered reactivity” of *whatever* origin. The term originally embraced both immunity and hypersensitivity. In 1925, European allergists influenced their American counterparts to redefine allergy in the context of antibodies and antigens. A few American allergists objected, observing that hypersensitivity in some patients could be occurring on a non-immunologic basis. In 1967, the discovery of IgE cemented the antibody-antigen definition of allergy into place, apparently permanently. Allergists have spent many hours instructing the MCS patients who consult them that what they have is not an allergy.

## 8. Association versus causation

Critics of MCS correctly observe that “humans have a desire to assign a cause for everything.” The history of mankind is filled with examples of man’s attempts to assign cause to every event, particularly to illness, misfortune, or death (Waddell, 1993). The question is, how do we distinguish between a chance association and true cause and effect? Sir Austin Bradford Hill (1965) offered nine criteria that have been widely used by epidemiologists to help make this distinction: (1) Strength of the association, i.e. between the exposure and the illness. For example, Percival Pott observed an enormous, perhaps 200-fold increase in scrotal cancer among chimney sweeps versus workers not exposed to tar or mineral oils, a strong association indeed. However, Hill cautions, we should not be too ready to dismiss a cause-and-effect hypothesis merely on the grounds that the observed association appears slight, because there are many instances in medicine when this occurs, yet a cause-and-effect relationship exists. For example, only a few persons who harbor meningococcus develop meningitis

from it, and only a few individuals who are stung by bees develop anaphylaxis. Analogously, only a few persons exposed to certain pesticides or a sick building appear to develop MCS.

(2) Consistency. Have different people in different places and times observed the association? Hill considers this especially important for rare hazards or conditions. With regard to chemical sensitivity, multiple observers have independently described chemical sensitivity arising in persons exposed to organophosphate pesticides (Rosenthal and Cameron, 1991; Cone and Sult, 1992; Miller and Mitzel, 1995).

(3) Specificity of the association. The more the association is limited to specific exposures and/or to specific types of disease, the clearer the case for causation. Research on inducing exposures for MCS might reveal strong, specific associations. With respect to triggering, there appears to be lack of specificity both in terms of exposures and symptoms. However *individual* MCS patients report specific symptoms with specific exposures. Unlike for cancer or heart disease, cause and effect for symptom triggering in MCS can be tested experimentally in humans, providing direct experimental measurement of the specificity of the association (if it exists), the strongest form of evidence possible for an environmentally-related illness.

(4) Temporality. Does the exposure precede the illness? Some authors have noted depression or somatoform tendencies in some MCS patients that preceded their "initiating" exposure event. Perhaps the strongest evidence for temporality is the temporal cohesiveness between exposure and onset of symptoms that has been observed in large exposure groups, for example, the Environmental Protection Agency's sick building occupants or the Gulf veterans, many of whom report new-onset intolerances and have no evidence of psychiatric problems predating their exposure.

(5) Biological gradient. An association that follows a biological gradient or dose-response curve strongly suggests causality. Hill acknowledges that it is frequently difficult to obtain a satisfactory measure of exposure. However, a dose-response relationship that has been inferred for allergic conditions (Waddell, 1993) may also per-

tain to chemical sensitivity: there is a dose-response relationship for the first, sensitizing exposure in a susceptible individual; with subsequent exposures, the now sensitized person also responds in proportion to the dose, but at a much lower dose level. In addition, MCS patients frequently report that the longer they remain in an exposure situation, the more severe their symptoms become and the longer they persist. Again, in contrast with cancer or other environmentally-related diseases, the triggering phase of chemical sensitivity lends itself to direct human testing of a dose-response relationship, thus obviating the need for speculation about a biological gradient.

(6) Plausibility. Hill comments that it is helpful if the causation we suspect is biologically plausible, but that *what is plausible depends upon the biological knowledge of the time*: "in short, the association we observe may be new to science or medicine and we must not dismiss it too lightheartedly as just too odd." In fact there are some medical conditions which have features that are strikingly similar to MCS and which are well-accepted, for example, Reactive Airways Dysfunction Syndrome (discussed previously) and Multiple Drug Allergy Syndrome (Sullivan, 1991). These parallel clinical observations may be signs pointing in the direction of biological plausibility for MCS.

(7) Coherence. The cause-and-effect relationship under scrutiny should not conflict with other generally known facts about the disease, e.g. the pathology or biochemistry of the illness. Since so little research has been done on MCS, so far this has not been a problem.

(8) Experiment. Experimental evidence can provide the strongest support for a cause-and-effect relationship. Perhaps one of the reasons MCS patients are so dogged in their insistence that chemicals are causing their symptoms is the strength of the experimental evidence they perceive when they deliberately avoid and then are re-exposed to incitants. Part of the appeal of MCS, at least to some environmental scientists, is that it poses an experimentally testable hypothesis, in contrast with most other environmentally-related illnesses of major concern. But, again, experimental conditions must be optimized, i.e.

unmasking in an environmentally-controlled hospital unit, if the most robust effect is to be seen. Currently, the *only* obstacle to these studies being undertaken is lack of funding.

(9) Analogy. Under certain circumstances, cause-and-effect can be inferred by analogy. The sensitivities reported by MCS patients are reminiscent of the heightened sensitivity to tobacco smoke reported by those who have recently quit smoking. Likewise, there are close parallels between MCS and addiction, in which food cravings and bingeing are also reported. MCS patients describe “going through withdrawal” or “detox” during which the symptoms they report are reminiscent of those reported by drug abusers, yet most MCS patients systematically avoid even mildly addictive substances. Other possible analogues to MCS are Reactive Airways Dysfunction Syndrome (RADS) and toluene diisocyanate (TDI) sensitivity, particularly the former in which a single major exposure may lead to hyperresponsiveness to multiple, chemically-unrelated inhalants. We must ask ourselves, if the airways can develop sensitivity to multiple chemicals, by analogy why couldn't the central nervous system do so as well?

To Hill's criteria, I might add a tenth criterion, one that would apply to symptoms (or illnesses) that are primarily subjective in nature:

(10) Unique symptomatology. The more obscure or unique a symptom is, particularly if it is reported by several independent exposure groups (for example, industrial workers, white collar professionals, Gulf veterans), the greater the likelihood of causation. For MCS, it would be difficult to imagine that the curious symptom of odor intolerance, which has been reported by demographically diverse groups following various exposure events, could be “invented” by all of them. Equally unexpected and counter-intuitive are MCS patients' practices of avoiding fragrances, foods, alcoholic beverages, etc., that they formerly relished. Why would anyone who really liked pizza, chocolate or beer give them up unless they made them ill? Why would a mechanic who loved his job and used to think that WD-40 would make a wonderful perfume, suddenly report that odors at work made him ill, if in fact they did

not? Why would doctors, lawyers, teachers and others say they quit their professions because of severe mental confusion around fragrances and engine exhaust, if this weren't the case? Scientifically, it would be absurd to dismiss such eccentric behaviors in otherwise sane individuals without searching exhaustively for a plausible biological basis.

Hill suggests that his criteria be used to “study association before we cry causation.” He further cautions that none of the criteria indisputably revokes a cause-and-effect hypothesis, and none is a *sine qua non*. In aggregate, these criteria assist in determining causation. As discussed previously, chemical sensitivity appears to involve two steps: Induction by a major or repeated exposure, and (2) subsequent triggering of symptoms by chemically-unrelated, low level exposures. Verification of the second of these two steps lends itself to direct experimental testing. Validation of the first step may rest upon epidemiological investigations and animal studies.

## 9. Conclusion

If we now begin to speak of chemical sensitivity—the theory of disease, instead of chemical sensitivity—the symptom or the syndrome, the types and number of individuals potentially affected by the condition shift dramatically. While roughly one-third of the population reports the *symptom* of chemical sensitivity, only a fraction of these individuals suffers from a *syndrome* that disrupts their health or lifestyle. In contrast, chemical sensitivity—the *theory of disease* posits that familiar, chronic conditions like depression, migraine, fatigue, and asthma can arise from environmental exposure. The health care costs associated with these conditions are undeniably enormous. Notably, many of these same conditions also appear to be becoming more prevalent, which should further pique our curiosity about environmental causation, particularly given the exponential increases in synthetic organic chemical and pesticide production that have taken place in this country since World War II, coupled

with the fact that most Americans spend 90% or more of their day indoors, often in tightly constructed buildings with poor air quality.

How we define and conceptualize chemical sensitivity drastically affects our perspective regarding the seriousness of “low level” environmental exposures. As a symptom, chemical sensitivity or pathosmia generally is not disabling; as a syndrome, multiple chemical sensitivity is uncommon (although if only 1% of Americans were affected, it would still amount to a few million people). Those who see chemical sensitivity as an emerging theory for disease see something profoundly different and deeply concerning.

Only carefully designed studies in a controlled environment will answer the complex questions before us concerning the environmental etiologies of many chronic diseases. Studies of this kind will be essential for determining what role toxicant-induced loss of tolerance plays, if any, in human disease. From the standpoint of public health, if it were to be determined that chemical sensitivity was limited to a small group of vulnerable individuals in the population, perhaps strategies for protecting or accommodating them could be devised, such as special ventilation, working at home, wearing respirators, etc. Indeed such things already are being done. On the other hand, if chemical sensitivity is an emerging theory of disease that applies not only to MCS, but also to depression, migraine, asthma, chronic fatigue syndrome, illnesses associated with implants, and other conditions, the stakes go up considerably. Medical care costs in this nation have risen from 5.3% of gross domestic product in 1960 to 13.9% in 1993, with a dollar value exceeding \$1 trillion, nearly \$4000 per person (Grumbach and Bodenheimer, 1994; Levit et al., 1994). An important question is, how much does toxicant-induced loss of tolerance contribute to this sum?

These are vexing questions that go against the grain of accepted explanations concerning the origins of illness. In recent times, many chronic diseases, addiction, and violence have been explained in whole or in part in terms of the psyche and stress. An enormous amount of research has been devoted to these explanations. There are

about 37 000 psychiatrists and 241 000 psychologists in the United States (Roback et al., 1994; Statistical Abstract of the United States, 1994). Any theory of disease so bold as to suggest that depression, anxiety, panic attacks or fatigue might be caused by chemical exposures should expect a less than enthusiastic reception. Yet, most would agree *in principle* that organic bases for illnesses should be ruled out before psychological explanations are invoked. In medicine, millions of dollars are devoted to the study of the chronic conditions discussed here and to identifying psychological therapies and drug interventions. Yet, *what if* such therapies alleviated some but not all symptoms, and in the meantime causative exposures were overlooked? Such a notion seems farfetched, yet it is precisely what some heretical scientists and physicians now propose. A skeptical regard for such speculation by most practitioners should be viewed as a rational response to the flurry of pronouncements and papers of varying reliability that have appeared on chemical sensitivity in recent years. Wherever the truth lies, the costs of not pursuing scientific resolution of these questions are potentially enormous.

Perspective is important. Finding a biological marker for chemical sensitivity may prove as difficult as finding the bacterium that was causing cholera or identifying IgE in allergic diseases. Generally speaking, treatment and intervention need not await the discovery of a marker. Hand washing, sanitation, and allergy shots were all introduced based on clinical observations. Physicians over the centuries have had to tolerate uncertainty and cautiously adopt new therapies while awaiting scientific explanations, but never before in a nation or time with such high-tech medical prowess and vested corporate interests, neither of which has much enthusiasm nor patience for chemical sensitivity.

Science is not about belief. Science is about “guess and test.” A new “guess,” perhaps an emerging theory of disease that parallels the germ theory, has come to our attention. The theory suggests that certain costly, chronic illnesses may be caused by familiar exposures. The theory insinuates that environmental exposures may

cause loss of tolerance for specific chemicals, foods and drugs, that is, toxicant-induced loss of tolerance. The question is, shall we expend scant resources to explore this theory, or will we continue the present debate?

“When I use a word,” Humpty Dumpty said, in rather a scornful tone, “it means just what I choose it to mean—neither more nor less.”

“The question is,” said Alice, “whether you can make words mean so many different things.”

“The question is,” said Humpty Dumpty, “which is to be master — that’s all.”

Lewis Carroll (emphasis added)

## References

- Agency for Toxic Substances and Disease Registry (1994) In: F.L. Mitchell and P. Price (Eds.), *Proceedings of the Conference on Low-Level Exposure to Chemicals and Neurobiologic Sensitivity*. *Toxicol. Ind. Health* 10, 253–669.
- Ashford, N.A. and Miller, C.S. (1989) *Chemical Sensitivity. A Report to the New Jersey State Department of Health*.
- Ashford, N.A. and Miller, C.S. (1991) *Chemical Exposures: Low Levels and High Stakes*, Van Nostrand Reinhold, New York.
- Association of Occupational and Environmental Clinics (AOEC) (1992). In: K.M. Rest (Ed.), *Proceedings of the AOEC Workshop on Multiple Chemical Sensitivity*. *Toxicol. Ind. Health* 8, 1–257.
- Bascom, R. (1989) *Chemical Hypersensitivity Syndrome Study. Options for Action: a Literature Review and a Needs Assessment. A Report to the State of Maryland Department of Environment*.
- Bell, I.R. (1994) Somatization disorder: healthcare costs in the decade of the brain. *Biol. Psychiatry* 35, 81–83.
- Bell, I.R., Schwartz, G.E., Amend, D., Peterson, J.M. and Stini, W.A. (1994) Sensitization to early life stress and response to chemical odors in older adults. *Biol. Psychiatry* 35, 857–863.
- Bell, I.R., Miller, C.S., Schwartz, G.E., Peterson, J.M. and Amend, D. (1995) Neuropsychiatric and somatic characteristics of young adults with and without self-reported chemical odor intolerance and chemical sensitivity. *Arch. Environ. Health* 51, 9–21.
- Carter, K.C. (1985) Ignaz Semmelweis, Carl Mayrhofer, and the rise of the germ theory. *Med. Hist.* 29, 33–53.
- Cone, J.E. and Sult, T.A. (1992) Acquired intolerance to solvents following pesticide/solvent exposure in a building: a new group of workers at risk for multiple chemical sensitivities? *Toxicol. Ind. Health* 8, 29–39.
- Cullen, M.R. (ed), (1987) *Workers with multiple chemical sensitivities*. *Occup. Med.* 2, 655–806.
- Environmental Protection Agency (1989) *Indoor Air Quality and Work Environment Study: EPA Headquarters' Buildings, Vol. I, Employee Survey*.
- Gots, R.E., Hamosh, T.D., Flamm, W.G. and Carr, C.J. (1993) *Multiple chemical sensitivities: a symposium on the state of the science*. *Regul. Toxicol. Pharmacol.* 18, 61–78.
- Grumbach, K. and Bodenheimer, T. (1994) Painful vs. painless cost control. *J. Am. Med. Assoc.* 272, 1458–1464.
- Hill, A.B. (1965) The environment and disease: association or causation? *Proc. R. Soc. Med.* 58, 295–300.
- Kuhn, T.S. (1970) *The Structure of Scientific Revolutions*, University of Chicago Press, Chicago.
- Levit, K.R. et al. (1994) *National Health Expenditures, 1993*. *Health Care Financ. Rev.* 16, 247–294.
- Meggs, W.J. and Cleveland, C.H. (1993) Rhinolaryngoscopic examination of patients with the Multiple Chemical Sensitivity Syndrome. *Arch. Environ. Health* 48, 14–18.
- Meggs, W.J. (1994) Self-reported prevalence of chemical sensitivity and allergy in Eastern North Carolina. Presented at the Am. Public Health Assoc. Meeting, Nov. 1994, Washington, DC. *Arch. Environ. Health* (in press).
- Miller, C.S. (1994) White paper. *Chemical sensitivity: history and phenomenology*. *Toxicol. Ind. Health* 10, 253–276.
- Miller, C.S. and Mitzel, H.C. (1995) Chemical sensitivity attributed to pesticide exposure versus remodeling. *Arch. Env. Health* 50, 119–129.
- Mitchell, F.L. and Price, P. (1994) *Proceedings of the conference on low-level exposure to chemicals and neurobiologic sensitivity*. *Toxicol. Ind. Health* 10, 253–669.
- Morrow, L.A., Ryan, C.M., Hodgson, M.J. and Robin, N. (1990) Alterations in cognitive and psychological functioning after organic solvent exposure. *J. Occup. Med.* 32, 444–450.
- National Research Council (NRC) (1992) *Multiple Chemical Sensitivities: Addendum to Biological Markers in Immunotoxicology*, National Academy Press, Washington, DC.
- Roback, G., Randolph, L., Seidman, B. and Pasko, T. (1994) *Physician Characteristics and Distribution in the U.S.*, American Medical Association, Chicago, p. 20.
- Rosenthal, N. and Cameron, C.L. (1991) Exaggerated sensitivity to an organophosphate pesticide (letter). *Am. J. Psychiatry* 148, 270.
- Ryan, C.M., Morrow, L.A. and Hodgson, M.J. (1988) Cacosmia and neurobehavioral dysfunction associated with occupational exposure to mixtures of organic solvents. *Am. J. Psychiatry* 145, 1442–1445.
- Sartin, J.S. (1993) Infectious diseases during the Civil War: the triumph of the “Third Army”. *Clin. Infect. Dis.* 16, 580–584.
- Statistical Abstract of the United States (1994) *Bernan Press*, Lanham, MD, p. 407.
- Stockholm International Peace Research Institute (SIPRI) (1975) *Delayed Toxic Effects of Chemical Warfare Agents*, Almquist and Wiskell International, New York.
- Sullivan, J.T. (1991) Management of patients allergic to antimicrobial drugs. *Allergy Proc.* 12, 361–364.

- Tabershaw, I.R. and Cooper, C. (1966) Sequelae of acute organic phosphate poisoning. *J. Occup. Med.* 8, 5–20.
- Waddell, W.J. (1993) The science of toxicology and its relevance to MCS. *Regul. Toxicol. Pharmacol.* 18, 13–22.
- Warner, M. (1985) Hunting the Yellow Fever germ: the principle and practice of etiological proof in late nineteenth-century America. *Bull. Hist. Med.* 59, 361–382.
- Webster's (1986) In: P.B. Gove (Ed.), *Webster's Third New International Dictionary of the English Language (Unabridged)*, Merriam-Webster, Springfield, MA.
- Woodbury, A.C. (1995) University of Texas at Austin, personal communication.