

The Compelling Anomaly of Chemical Intolerance

CLAUDIA S. MILLER^a

Environmental and Occupational Medicine, Department of Family and Community Medicine, University of Texas Health Science Center at San Antonio, San Antonio, Texas 78229-3900, USA

It may be the all-inclusiveness of potential factors, the difficulty of establishing an animal model, and the lack of measurable endpoints that make acceptance of the hypothesis difficult. It would seem as if almost any combination [of chemicals] that every human being is exposed to might initiate this sequence, and almost any factor may trigger it once established. Therefore, is it the agents or the responder?

—FREDERICK F. BECKER (LETTER TO THE AUTHOR)
University of Texas MD Anderson Cancer Center

ABSTRACT: In science, anomalies expose the limitations of existing paradigms and drive the search for new ones. In the late 1800s, physicians observed that certain illnesses spread from sick, feverish individuals to those contacting them, paving the way for the germ theory of disease. The germ theory served as a crude, but elegant formulation that explained dozens of seemingly unrelated illnesses affecting literally every organ system. Today, we are witnessing another medical anomaly—a unique pattern of illness involving chemically exposed groups in more than a dozen countries, who subsequently report multisystem symptoms and new-onset chemical, food, and drug intolerances. These intolerances may be the hallmark for a new disease process or paradigm, just as fever is a hallmark for infection. The fact that diverse demographic groups, sharing little in common except some initial chemical exposure event, develop these intolerances is a compelling anomaly pointing to a possible new theory of disease, one that has been referred to as “Toxicant-Induced Loss of Tolerance” (“TILT”). TILT has the potential to explain certain cases of asthma, migraine headaches, and depression, as well as chronic fatigue, fibromyalgia, and “Gulf War syndrome”. It appears to evolve in two stages: (1) *initiation*, characterized by a profound breakdown in prior, natural tolerance resulting from either acute or chronic exposure to chemicals (pesticides, solvents, indoor air contaminants, etc.), followed by (2) *triggering* of symptoms by small quantities of previously tolerated chemicals (traffic exhaust, fragrances, gasoline), foods, drugs, and food/drug combinations (alcohol, caffeine). While the underlying dynamic remains an enigma, observations indicating that affected individuals respond to structurally unrelated drugs and experience cravings and withdrawal-like symptoms, paralleling drug addiction, suggest that multiple neurotransmitter pathways may be involved.

^aAddress for correspondence: Environmental and Occupational Medicine, Department of Family and Community Medicine, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78229-3900. Voice: 210-567-7760; fax: 210-567-7764. millercs@uthscsa.edu

Scientific understanding of chemical intolerance remains in its infancy, mired in controversy. The media tends to fuel the controversy by portraying only the most extreme cases, overlaid with a thin veneer of scientific opinion. Patients with this problem are caught up in the acrimonious cross fire between various physician groups. This acrimony is fueled by the different medical paradigms concerning the condition's origins. Litigation and compensation claims lead to adversarial proceedings that draw medical practitioners unwillingly into the conflict. Expert witnesses paint themselves into scientific corners and opinions harden on all sides. Everyone has an opinion, mostly based upon their personal beliefs with no definitive data to support them. However, science is not about belief. It is about "guess and test", that is, formulating hypotheses based upon observation ("guess") and then testing those hypotheses ("test"). All science begins with observation.

The purpose of this paper is to summarize the available, salient observations concerning chemical intolerance. Admittedly, most of these observations are anecdotal. This is normal for new science. The observations presented here constitute the few facts available to us, but there is considerable agreement about them. The next step is formulating a hypothesis that explains these observations, a process that Darwin described as "grouping facts so general laws can be derived from them". Comprehensive fact-gathering is the first critical step. Done well, it will enable us to avoid what Thomas Henry Huxley called "the great tragedy of science—the slaying of a beautiful hypothesis by an ugly fact". In the next section, we will review the "ugly facts" of chemical intolerance, those which any successful hypothesis must be able to explain.

THE UGLY FACTS

Roughly half of those who are chemically intolerant say their illness began following a specific exposure event, referred to as an *initiating* event, for example, a chemical spill, chronic solvent exposure, a pesticide application, indoor air contaminants, combustion products, etc. (FIG. 1).¹ A small subset of individuals exposed in situations like these appear to develop chronic symptoms that persist years, even decades, beyond their original exposure. At first, affected individuals may describe "flu-like" symptoms that just will not go away, or feeling as though they are in a "perpetual fog". Next to develop are multisystem symptoms that seem to wax and wane unpredictably. Subsequently, there may be a dawning awareness of certain new intolerances, for example, for alcoholic beverages or a medication. Over time, these intolerances grow to include a wide variety of common, structurally unrelated chemicals, foods, drugs, caffeine, alcoholic beverages, and skin contactants. This has been termed the "spreading phenomenon". The intolerances may appear suddenly, within weeks following an acute, high-level exposure (e.g., a chemical spill), or, in the case of lower level exposures (e.g., a sick office building), develop insidiously over months or years.

Food intolerances may develop, but go unrecognized at first. Affected individuals may instead report every sort of digestive difficulty, feeling ill after meals, or extreme irritability if a meal is missed or delayed. Symptoms can occur following inhalation, ingestion, mucosal contact, or injection (e.g., drugs) of a substance. Different exposures, for example, fragrances, chemicals outgassing from new fur-

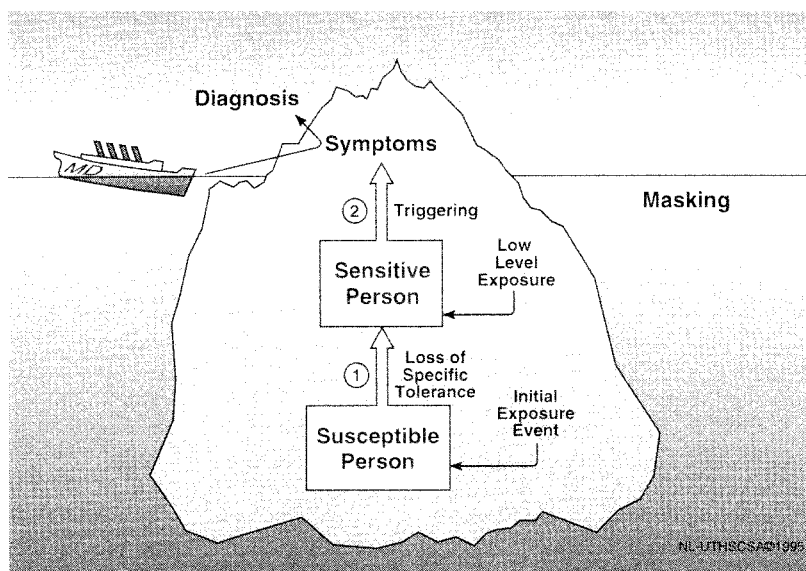


FIGURE 1. Phenomenology of Toxicant-Induced Loss of Tolerance (TILT). Illness appears to develop in two stages: (1) initiation, that is, loss of prior, natural tolerance resulting from an acute or chronic exposure (pesticides, solvents, indoor air contaminants, etc.), followed by (2) triggering of symptoms by small quantities of previously tolerated chemicals (traffic exhaust, fragrances), foods, drugs, and food/drug combinations (alcohol, caffeine). The physician sees only the tip of the iceberg—the patient’s symptoms—and formulates a diagnosis based on them (e.g., asthma, depression, chronic fatigue, migraine headaches). Masking hides the relationship between symptoms and triggers. The initial exposure event causing breakdown in tolerance also may go unnoticed (©UTHSCSA 1996).

nishings or carpeting, traffic exhaust, cleaning agents, etc., may trigger different constellations of symptoms that vary from person to person (TABLE 1). There is a certain consistency to these complaints: A *particular* exposure (e.g., diesel exhaust or a fragrance) in a *particular* person is said to elicit a characteristic constellation of symptoms—a *signature response* for that person with that exposure. These responses can occur at below-olfactory-threshold concentrations. Symptoms may flare seconds to hours after a triggering exposure and persist for minutes to days. Patients may report that certain symptoms enable them to identify a specific trigger (e.g., a pesticide), even when no odor is apparent. Hyperresponsiveness to physical stimuli, including bright light, noise, and touch, is commonly reported.^{2,3} People who lack a sense of smell (anosmic individuals) may also suffer from chemical intolerances.

Affected individuals generally report that avoiding problem exposures, including foods that bother them, offers relief.⁴ In fact, most patients claim that avoidance is the only “treatment” that reliably helps them.⁵ Low-level volatile organic chemical (VOC) concentrations in the parts per billion (ppb) or parts per trillion (ppt) range are nearly ubiquitous, making avoidance difficult, as well as socially isolating. Daily exposure to various chemical, food, and drug triggers may hide or “mask” the symp-

TABLE 1. Symptoms commonly reported by chemically intolerant individuals¹¹

<i>Neuromuscular</i>	<i>Cardiac</i>
Loss of consciousness	Heart pounding
Stumbling/dragging foot	Rapid heart rate
Seizures	Irregular heart rate
Print moving/vibrating on page	Chest discomfort
Feeling off balance	
Tingling in fingers/toes	<i>Affective</i>
Double vision	Feeling tense/nervous
Muscle jerking	Uncontrollable crying
Fainting	Feeling irritable/edgy
Numbness in fingers/toes	Depressed feelings
Clumsiness	Thoughts of suicide
Problems focusing eyes	Nerves feel like vibrating
Cold or blue nails/fingers	Sudden rage
Uncontrollable sleepiness	Loss of motivation
	Trembling hands
	Insomnia
<i>Head-related</i>	
Head fullness/pressure	
Tender face/sinuses	<i>Airway</i>
Sinus infections	Cough
Tightness in face/scalp	Bronchitis
Brain feels swollen	Asthma or wheezing
Ringing in ears	Postnasal drainage
Headache	Excessive mucus production
Feeling groggy	Shortness of breath
	Eye burning/irritation
	Susceptible to infections
<i>Musculoskeletal</i>	Dry eyes
Joint pain	Enlarged/tender lymph nodes
Muscle aches	Hoarseness
Weak legs	
Weak arms	<i>Cognitive</i>
General stiffness	Memory difficulties
Cramps in toes/legs	Problems with spelling
Painful trigger points	Slowed responses
	Problems with arithmetic
<i>Gastrointestinal</i>	Problems with handwriting
Abdominal gas	Difficult concentration
Foul gas	Difficulty making decisions
Problems digesting food	Speech difficulty
Abdominal swelling/bloating	Feelings of unreality/spacey
Foul burping	
Diarrhea	
Abdominal pain/cramping	<i>Other</i>
Constipation	Feeling tired/lethargic
	Dizziness/lightheadedness

NOTE: Categories were derived via factor analysis of symptoms reported by 112 individuals who said they became ill following exposure to indoor air contaminants ($n = 75$) or cholinesterase-inhibiting pesticides ($n = 37$).

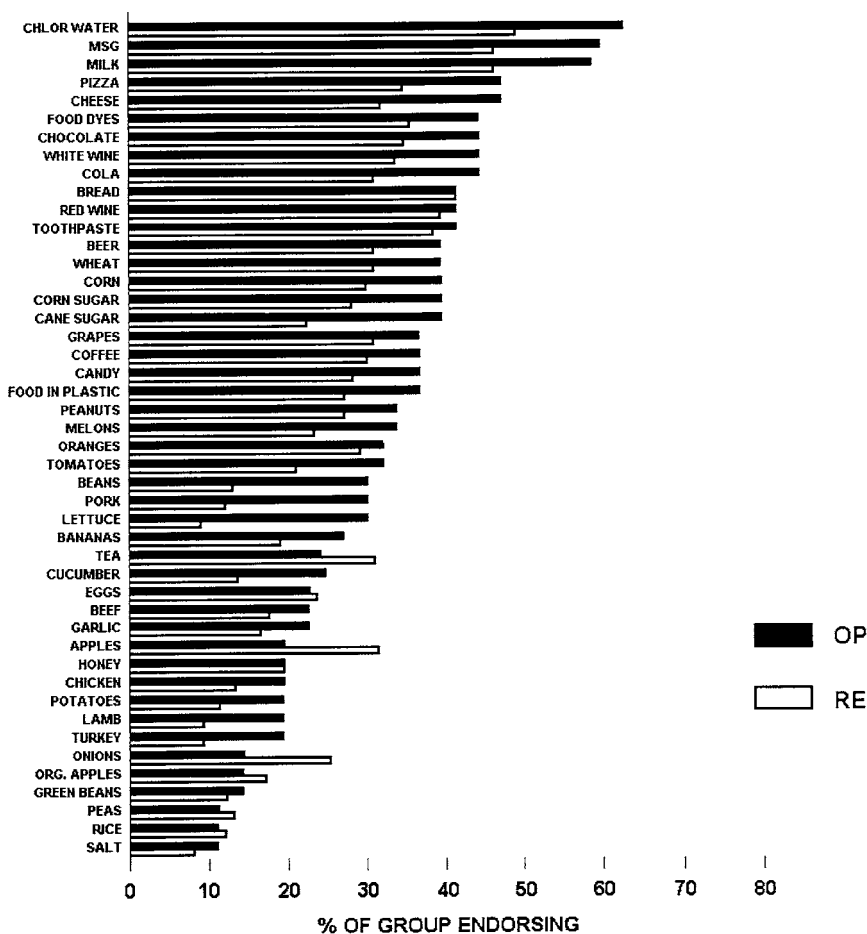


FIGURE 2. Organophosphate-exposed (OP) versus remodeling-exposed (RE): comparison of endorsement rates for all ingestant items.¹¹

toms caused by any individual exposure (FIG. 2). For example, a person who uses hair spray and fragrances in the morning, cooks breakfast on a gas stove, and drives through heavy traffic to work in a sick office building may experience near-continuous symptoms.^{6,7}

Complicating matters further, repeated exposures (those occurring twice a week or more often) to the *same* trigger, whether indoor air contaminants or caffeine, can cause *habituation*, further obfuscating symptom-exposure relationships. Together, masking and habituation may make it difficult for physicians, and even the patients themselves, to recognize particular triggers. “Withdrawal” symptoms may develop when patients avoid their problem exposures for several days, for example, over a weekend or during a vacation. With reexposure, for example, Monday morning after resuming work, symptoms may return “with a vengeance”. Patients sometimes quit

their jobs to avoid fragrances, carbonless copy paper, cleaning agents, etc. Others switch employers, occupations, and residences in search of safer surroundings.

About 80% of patients who have participated in clinical studies have been women, with an average age in the fourth decade and educational level of at least two years of college.⁸ Among military and industrial populations, primarily males report the problem, likely reflecting underlying gender ratios.^{2,3,9} A question remains as to whether females may be disproportionately affected even in these groups. In sick building situations, the condition is more commonly reported by college-educated white females in the middle-age range (30–50 years) and of middle to upper-middle class socioeconomic status.¹⁰ It remains a mystery why more chemically intolerant patients work in office buildings and service industries than in heavy industry where chemical exposures are considered more common, and why more women than men report the problem.^{4,11,12} Gender differences may be the result of male/female differences in willingness to report symptoms, something unique about indoor air pollutants present in offices where women tend to be relatively more confined (e.g., as secretaries), or gender-based biological response differences. The paradox that more multiple chemical intolerance cases arise from service industries than heavy industries may be due to “the healthy worker” selection effect, that is, individuals bothered by chemical exposures tend to choose nonchemical jobs; the fact that women, who may be biologically more vulnerable, are less apt to work in heavy industry, mining, construction, etc.; or some unknown, but insidious effect of indoor air chemicals.

A recent, statewide California Department of Health Services study, involving randomized telephone interviews of more than 4000 people, found that both female gender and Hispanic ethnicity were associated with increased self-reporting of chemical intolerance (adjusted odds ratios of 1.63 and 1.82, respectively).¹³ As opposed to most clinical studies on chemical intolerance, the California survey did not find employment or education to be associated with chemical sensitivity or doctor-diagnosed MCS; nor was multiple chemical intolerance associated with marital status, geographic location, or income.

People who become chemically intolerant may have had more health problems even before their initial exposure than similarly exposed individuals who do not get sick. For example, aerospace workers who became ill following the introduction of new composite plastic in their workplace averaged 6.2 unexplained physical symptoms *preceding* the change in process versus 2.9 unexplained symptoms in unaffected coworker controls.⁹ Fifty-four percent of the chemically intolerant workers had histories of anxiety or depression that preceded their exposure, compared with 4% of controls. Other researchers find that past psychiatric history does not explain the illness.¹⁴ Even if some chemically intolerant individuals do experience depression that predates their initial exposure, the question remains whether their intolerances are caused by depression, whether they are more vulnerable to developing intolerances as a result of preexisting depression (e.g., due to altered brain neurochemistry), or whether their preexposure depression may have resulted from earlier unidentified intolerances.¹⁵

Most chemically intolerant individuals report multisystem symptoms, with fatigue being the most common (TABLE 2). Symptoms often mimic chronic fatigue syndrome and fibromyalgia, diagnoses many patients eventually acquire.^{10,11,16,17} Mood changes (irritability, anxiety, depression) are commonly reported. Gulf War

TABLE 2. Top 20 symptoms (of 119 symptoms) reported by MCS patients attributing their illness to pesticides ($n = 37$) versus remodeling ($n = 75$)¹

Symptom	Ranking		Mean symptom severity ^a	
	Pesticide	Remodel	Pesticide	Remodel
Tired or lethargic ^b	1	1	2.49	2.44
Fatigue > 6 months ^b	2	3	2.43	2.10
Memory difficulties ^b	3	4	2.32	2.09
Difficulty concentrating ^b	4	2	2.32	2.17
Dizziness, lightheadedness ^b	5	6	2.19	1.85
Depressed feeling ^b	6	8	2.19	1.83
Spacey ^b	7	12	2.19	1.74
Groggy ^b	8	5	2.14	1.96
Loss of motivation ^b	9	7	2.11	1.84
Tense, nervous ^b	10	15	2.11	1.64
Short of breath ^b	11	18	2.11	1.61
Irritable ^b	12	10	2.03	1.79
Problem focusing eyes	13	43	2.03	1.27
Chest pain	14	52	2.00	1.19
Muscle aches ^b	15	11	2.00	1.79
Problems digesting food	16	33	1.97	1.35
Joint pain ^b	17	9	1.95	1.83
Tingling fingers/toes	18	59	1.95	1.12
Headaches ^b	19	14	1.92	1.67
Head fullness or pressure ^b	20	19	1.92	1.60
Difficulty making decisions	21	13	1.89	1.69
Eye irritation	22	16	1.89	1.64
Slowed response	34	17	1.72	1.63
Nausea	36	20	1.65	1.56

NOTE: See reference 1.

^aSymptoms scored on a 0-to-3 scale: 0 = not a problem; 1 = mild; 2 = moderate; 3 = severe.

^bAmong top 20 symptoms in both pesticide and remodeling patients.

veterans may report sudden rage after particular exposures, a phenomenon referred to as “short fuse syndrome”. Fearing they might harm their families, some have handed their guns over to friends for safekeeping. Exposure-related memory and concentration difficulties have led teachers, attorneys, executives, nurses, and other professionals to abandon their cognitively demanding careers.

Different exposure *groups* with different “initiating” exposures describe surprisingly similar symptoms: We compared symptoms reported by 75 chemically intolerant individuals who became ill following building remodeling and 37 who became ill after exposure to a cholinesterase-inhibiting pesticide. Symptoms, ranked in order by severity, were remarkably similar for the two groups, with central nervous system symptoms leading the list. The most common gastrointestinal complaint was “problems digesting food” and the most frequent respiratory complaint was “shortness of breath or being unable to get enough air”.¹¹

A COMPELLING ANOMALY

In 1989, in a report on multiple chemical intolerance for the New Jersey State Department of Health, Nicholas Ashford and I reviewed the published and “gray” literature in this area and interviewed doctors with divergent views. Our report identified four demographic groups in which “heightened reactivity” to chemicals had been documented:

- (1) industrial workers;
- (2) occupants of sick buildings, including office workers and school children;
- (3) residents of communities with chemically contaminated air or water;
- (4) individuals exposed to various chemicals in domestic indoor air, pesticides, drugs, and consumer products.

Although these groups differed greatly in terms of professional and educational attainment, age and sex, and the mix and levels of chemicals involved, we were struck by the fact that individuals in such demographically divergent groups reported similar polysymptomatic complaints triggered by chemical exposures. It suggested to us that perhaps some common thread united these individuals. The similarities between their medical complaints and their exposure histories appeared to be more than coincidental.

Subsequently, with support from the Agency for Toxic Substances and Disease Registry, Howard Mitzel and I conducted an *exposure-driven* study, comparing the outcomes for two well-defined exposure groups: chemically intolerant individuals ($n = 37$) who attributed their illness to a cholinesterase-inhibiting pesticide exposure (an organophosphate or carbamate) and a second group ($n = 75$) who attributed their intolerances to indoor air VOCs associated with new construction or remodeling. We hypothesized the following: if neurotoxic exposures caused multiple chemical intolerance, then the organophosphate group should report more severe symptoms than the VOC group since cholinesterase inhibitors are generally considered more neurotoxic than indoor air VOCs. Indeed, this turned out to be the case. Further, if the condition was caused by chemical exposures, we reasoned that there should be intergroup differences in symptom patterns and severity that reflected the original exposures. Again, the data confirmed significantly greater symptom severity in the pesticide-exposed group than in the VOC group, especially for neuromuscular, affective airway, gastrointestinal, and cardiac symptoms. Cognitive symptoms received the highest mean severity rating for both groups, whereas the largest intergroup difference occurred for cardiac symptoms. Overall, however, *symptom patterns* were near-identical (symptoms in same rank order) for the two groups and they identified similar inhalant and ingestant triggers (TABLE 3, FIG. 2). The fact that the *ordering* of chemical and food intolerances was almost the same for the two groups led us to conclude that, once the illness develops, “similar kinds of substances will trigger symptoms, *irrespective of the chemical nature of the original exposure*” [emphasis added].

Eighty percent of the pesticide and VOC groups were women with an average educational level of almost four years of college. There were no gender-related differences in symptom severity. The vast majority (97%) of participants identified one or more problem foods or other ingestants (e.g., chlorinated tap water, MSG). Sixty percent felt that their diets had been affected “a great deal”.

TABLE 3. Inhalant intolerances reported by 80% or more of 112 individuals attributing onset of their illness to organophosphate/carbamate pesticide exposure or indoor air VOCs¹¹

Nail polish remover
New carpeting
Detergent aisle in grocery store
Insecticide
Fresh newspaper, newsprint
Felt-tip dry-erase marking pen
Poorly ventilated meeting room
New automobile interior
Fabric store
Hotel room
Perfume
Cigarette smoke
Diesel exhaust
Asphalt or tar
Restroom deodorizer
Particle board
Traffic exhaust
Cigar smoke
Hair spray
Fresh latex paint

Around this same time, Ashford led a nine-country European exploratory study on multiple chemical intolerance, assembling an international research team with expertise in toxicology, occupational medicine, indoor air chemistry, environmental and occupational health, law, and sociology. Just as in the United States, they found that “initiating” exposures involving pesticides were common in Europe. Organic solvent initiating exposures were identified in all nine countries, most involving chronic exposures, that is, repeated solvent use, rather than acute ones. However, there were also potentially informative differences between countries. For example, pesticides were not implicated in Sweden, Finland, or the Netherlands, where cooler temperatures help control insect populations. A so-called “wood preservative syndrome”, attributed to pentachlorophenol that had been used to preserve wood for log homes, appeared only in Germany.¹⁸ Although Sick Building Syndrome (SBS) is widely recognized in Scandinavia, it is not commonly associated with multiple chemical intolerance cases in that region. Perhaps this is because Scandinavians are less likely to use pentachlorophenol or pesticides indoors. Scandinavians do, however, associate multiple chemical intolerance with new carpet installation.

In 1993, the chief of staff of the Houston Veterans Administration Hospital asked me to evaluate the first Gulf War veteran referred to their regional center for sick Gulf War veterans. The veteran’s principal problem was chemical intolerances. He was experiencing multisystem symptoms with exposures to a host of common chemicals, foods, and medications. After this veteran, I was asked to see the next 58 con-

secutive Gulf War veterans referred to the center, representing 17 states and a broad cross section of active-duty soldiers and reservists who served in different capacities and locations throughout the Persian Gulf. After reviewing these veterans' exposure histories, it became apparent that no *single* exposure was responsible for their health problems. Other researchers and expert panels have reached the same conclusion.

The different specialists these veterans see assign different labels to their symptoms: a rheumatologist observing diffuse muscle pain diagnoses myalgias; a neurologist hearing head pain and nausea diagnoses migraine headaches; a pulmonologist finding airway reactivity diagnoses asthma; a psychiatrist seeing chronic malaise diagnoses depression; a gastroenterologist noting GI complaints diagnoses irritable bowel syndrome. Nearly all of the veterans seen at the center had symptoms involving several organ systems simultaneously. For these veterans, there was no unifying diagnosis, no known etiology, and no single identifiable disease process. This is not the first time doctors have found themselves baffled by wartime disease. During the Civil War, doctors were faced with a similarly mysterious "syndrome" characterized by fever. Hundreds of thousands of soldiers died. The doctors did what good epidemiologists do today. They classified the cases. Since the hallmark symptom was fever, they classified the cases by fever type—remittent, intermittent, or relapsing. In doing so, they naively lumped together dozens of unrelated illnesses—everything from typhus and typhoid to malaria and tuberculosis.¹⁹ Who would have dreamed it—this germ theory of disease?: this war going on between invisible invaders and the body's immune defenses, with the only outward sign being—literally—the heat of battle.

Is it possible that we are facing the same situation with the Gulf War veterans?: only this time, the hallmark symptom is the newly acquired intolerances these veterans are experiencing—like the mechanic who used to "bathe" in solvents, but now becomes ill after one whiff of gasoline; or the young woman soldier who used to drink any man in her company under the table, but since the war cannot take even one drink without becoming violently ill. The vast majority of sick veterans interviewed reported these same newly acquired intolerances.

During my tenure as environmental medical consultant to the VA referral center, approximately 90% of veterans interviewed described new-onset intolerances to everyday chemical exposures that set off their symptoms: 78% were intolerant of fragrances, tobacco smoke, gasoline vapors, etc.; 78% described food intolerances; 66% reported alcohol intolerance; 25% were intolerant of caffeine; and nearly 40% reported adverse reactions to medications—all since the Gulf War. These intolerances, resulting in flare-ups of symptoms, including fatigue, headaches, GI problems, mood changes, cognitive impairment, and diffuse musculoskeletal pain, are like the fevers experienced by the Civil War soldiers—they are the outward manifestation of the underlying disease process.

What unites the Gulf War veterans and the civilian groups we have studied is their common experience of an initiating chemical exposure followed by newly acquired intolerances and multisystem symptoms. These observations provide compelling scientific evidence for a shared, underlying disease mechanism—one involving a *fundamental breakdown in natural tolerance*. This two-step process—an initiating toxic exposure followed by newly acquired intolerances that subsequently trigger multisystem symptoms—has been referred to with the acronym "TILT", or Toxicant-Induced Loss of Tolerance^b (FIG. 1).^{7,20–23}

This process is the key to understanding these illnesses. It does not appear to matter which exposure caused the breakdown in tolerance—be it pesticides, solvents, smoke from oil fires, or pyridostigmine bromide pills; those substances have long since left these people's bodies. It is the aftermath of these exposures, the new-onset intolerances to low-level chemical exposures, that appear to be perpetuating their symptoms. In some cases, it may be difficult to sort out individual intolerances or "triggers" because of "masking", the confusion of overlapping symptoms that results when individuals are responding to many everyday exposures.

However, the confusion clears when the underlying paradigm is understood. Thus, questions that could not be answered are answered: For example, why is there no generally accepted case definition for multiple chemical intolerance? The diverse symptoms these patients report have thwarted any such case definition attempts, which is to be expected if one is dealing with an entirely new *class of diseases*, paralleling other disease classes such as infectious diseases or immunological diseases.^c Or, how can structurally unrelated chemicals trigger symptoms, an observation that runs counter to toxicology and allergy as we currently understand them? Once more, if what we are dealing with is a new general disease mechanism, then diverse chemical agents might act as initiators, just as diverse pathogens cause infection and fever.

TILT also explains the following:

- Why affected individuals might remain sick for years after their initial exposure—as a consequence of subsequent triggering by everyday exposures.
- Why some symptoms wax and wane in such a bewildering fashion—as exposures and masking vary over time.

^bThe term "Toxicant-Induced Loss of Tolerance" describes a breakdown in prior innate tolerance, like a diabetic's loss of tolerance for sugar. When addictionologists use the term "tolerance", they mean "acquired tolerance", as in an addict following repeated drug use. Here, when we use "tolerance", we mean "natural tolerance". We refer to "habituation", instead of "acquired tolerance", when describing the diminished effect of an agent on a host following repeated administration. Semantics in this realm are difficult, a common problem for new paradigms. Addictionologists use the term "sensitization" to describe an individual's heightened responses following repeated exposure to a drug. Allergists, on the other hand, strenuously object to using "sensitization" in this manner because there is no evidence that heightened responses to most chemicals are immune-mediated. Instead, the allergists invoke the term "intolerance" for non-immunologic adverse responses. With TILT, we prefer the terms "tolerance" and "loss of tolerance" for several reasons: (1) most physicians and laypersons readily grasp the concept; (2) the body's natural ability to tolerate a wide variety of environment exposures is what appears to be lost; and (3) we are at a loss to find another readily recognizable term to convey this concept, short of inventing a new one.

^cMost proposed case definitions for multiple chemical intolerance (summarized in ref. 10) embody the same principal criteria: chronic, multisystem symptoms triggered by diverse, low-level chemical exposures, with symptoms resolving when exposures are avoided. A recent paper²⁴ proposes six "consensus criteria" based upon a survey of 89 clinicians and researchers familiar with, but having divergent views of, the illness:²⁵ (1) a chronic condition (2) with symptoms that recur reproducibly (3) in response to low levels of exposure (4) to multiple unrelated chemicals and (5) improve or resolve when incitants are removed (6) with symptoms that occur in multiple organ systems. The authors urge that multiple chemical intolerance be formally diagnosed *in addition to* any other diagnosable disorders (e.g., migraine, asthma, depression) in all patients in whom the above six criteria are met and for whom "*no single other organic disorder ... can account for all the signs and symptoms associated with chemical exposure.*"

- Why researchers have been unable to isolate a single culprit exposure underlying Gulf War “syndrome”—perhaps a wide variety of exposures culminate in TILT, with individual susceptibility determining who gets sick.

What can be done to diagnose and treat the chemically intolerant? An abundance of anecdotal evidence suggests the chemically intolerant improve when they become aware of what exposures are setting them off and learn to avoid those exposures. To this end, further studies are required using an environmental medical unit (EMU). This EMU is an environmentally controlled inpatient hospital unit where patients can be taken to a “clean” baseline so that their exposure-related symptoms will disappear. The patients can then be exposed to various potential triggers, including caffeine, gasoline, perfume, various foods, medications, and tobacco smoke, one at a time, to determine what is causing their symptoms. Funding for such an EMU is currently being considered.

A validated questionnaire (see APPENDIX) has been described in the medical literature and is currently available for purposes of diagnosis and evaluation of chemically intolerant individuals, as well as aiding researchers in the selection of patients and controls for studies.

To date, researchers have described this phenomenon—groups of individuals developing multisystem symptoms and new-onset intolerances following an initial chemical exposure event—in more than a dozen industrialized countries, including the United States, Canada, Australia, New Zealand, and nine European nations.^{10,26} These groups include the following: radiology workers from New Zealand and elsewhere exposed to X-ray developer solution containing glutaraldehyde and other solvents;²⁷ federal employees in the EPA headquarters building in Washington, D.C., exposed to volatile organic chemicals outgassing from new carpet and construction materials;^{28,29} German home owners exposed to pentachlorophenol wood preservative used in log homes;³⁰ sheep dippers in Great Britain exposed to organophosphate pesticides;^{10,31,32} hospital workers in Nova Scotia exposed to building air contaminants;¹⁰ and casino card dealers in Lake Tahoe, Nevada, exposed to solvents and pesticides,³³ among others.

As Kuhn notes, science begins with a list of observations like those we have just summarized.³⁴ Patterns then emerge. Next, scientists develop a model that forms their observations into a “coherent whole” for purposes of study. Mounting evidence supports TILT as a model for multiple chemical intolerance:

- The fact that the similar multisystem symptoms and new-onset intolerances have appeared in different demographic groups in more than a dozen countries following well-defined exposures to pesticides, solvents, indoor air contaminants, etc.
- The fact that these new-onset intolerances are not limited to chemical inhalants, but also involve foods, caffeine, alcohol, medications, and skin contactants.
- Striking parallels between this phenomenon and addiction (discussed further below), suggesting shared neural mechanisms.⁷
- The identification of an anatomical substrate—the nervous system—whose malfunction may explain these problems.
- Recent animal models replicating features of TILT.^{35–37}

ADDICTION AND ABDICTION

Randolph was first to observe the striking similarities between chemical intolerance and drug addiction. Both conditions, he noted, are characterized by stimulatory and withdrawal symptoms, cravings, and cross-addiction/intolerances to structurally diverse substances. One theory is that *both* addiction and chemical intolerance (or “abduction”) might involve loss of tolerance, whether due to repeated drug use or chemical exposures, resulting in amplification of stimulatory and withdrawal symptoms.^{7,22} Addicts become addicted, in part, in order to avoid unpleasant withdrawal symptoms. In contrast, chemically intolerant individuals, once they identify specific triggers, tend to avoid them, but *for the same reason addicts remain addicted—in order to avoid unpleasant withdrawal symptoms*. Initially, many chemically intolerant individuals consume caffeine, unaware that it may bother them. In fact, they may experience an initial brief lift, but overlook caffeine withdrawal symptoms occurring days later. Could it be that these apparent polar opposites—addiction and abduction—are in fact mirror-image strategies for avoiding withdrawal symptoms resulting from TILT?^{21,22}

While it seems almost inconceivable that here, in the twenty-first century, we would only now be stumbling upon a new theory of disease, it is worth remembering that other two-step theories of disease now widely accepted, that is, carcinogenesis and the immune theory of disease, were just as controversial in the past century.

CHALLENGES

Various economic interests have hindered research in this area. Some companies hire physicians and researchers as expert witnesses or sponsor their own scientific meetings in an effort to protect vested financial interests. It is the tobacco wars all over again, this time involving not one industry, but a host of industries, including carpet and rug manufacturers, fragrance makers, pesticide producers, building owners’ associations, etc.

There is little economic incentive to look further into the condition. Researchers, who respond lemming-like to funding opportunities, find scant opportunities in this realm. Medical research support comes from government sources (e.g., NIH) and pharmaceutical manufacturers, neither of which has shown much interest in this problem. Drug companies and government agencies can hardly be expected to invest in an illness whose very existence remains in doubt. Pharmaceutical companies are often owned by chemical corporations whose products patients may have blamed for causing their illness. Even if this were not the case, one could hardly expect pharmaceutical manufacturers to support research to help people who have trouble tolerating drugs.

Despite significant controversy and funding concerns, multiple chemical intolerance may be one of the most challenging and important puzzles that a researcher could tackle, for several reasons. First, it suggests a new theory of disease, one that has the potential to explain a wide variety of common illnesses whose prevalence has been increasing in recent decades (FIG. 3). Second, multiple chemical intolerance may be a very prevalent problem, perhaps the most common chemically induced illness in the United States. The California Department of Health Services’ chemical

intolerance prevalence study, a randomized sample of more than 4000 people, found that 6.3% reported having a physician's diagnosis of multiple chemical sensitivity or environmental illness.¹³ Some researchers feel this is an underestimate because people may be oblivious to system-exposure relationships due to the masking phenomenon.

Researchers at this meeting will be proposing specific mechanisms for multiple intolerances. Their hypotheses must embrace all of the salient observations for this condition, not just a subset of them. A recent newspaper notice announced, "Industrial Boulevard is empty because it is a road to nowhere. Work is under way to extend it." If the hypotheses proposed here fail to fit *all* of the salient observations concerning this condition, we will be on the road to nowhere too.

At present, stress and its role in this and other illnesses is a favored funding area. There is no question that these patients' symptoms look exactly like those we associated with stress—headaches, fatigue, irritability, depression, and memory and concentration difficulties. There is an understandable tendency to attribute the illness to stress, particularly when existing paradigms do not explain what we are seeing. We must not forget, however, that tens of thousands of chemically intolerant individuals, many holding advanced degrees, are telling us, as loudly and clearly as they can, that *chemical exposures directly and reproducibly* cause their anxiety, headaches, fatigue, irritability, depression, short-term memory difficulties, etc. Thus, we are in a chicken-and-egg situation here. If I have one major bias, it is against the current tendency to zero in on psychological explanations for this illness, when what we need to do is to back up and test the pivotal question first—that is, "is there a subset of people who respond adversely to extraordinary low levels of common chemicals, foods, and drugs?"

Many well-intentioned and well-credentialed researchers stand ready to study the role of stress in this condition. They apply for grants. Peer review committees and government panels meet to decide which studies will be funded, but most lack adequate understanding of the problem. Which studies do you think they will fund? There are approximately 37,000 psychiatrists and 241,000 psychologists in the United States.^{38,39} Any suggestion that chemical exposures might cause psychological symptoms can expect a less than enthusiastic reception.

Several government-sponsored consensus workshops have recommended that, as a first step, the EMU studies be conducted to determine whether these people are responding to low-level exposures. For research purposes, challenges would be done in a double-blinded, placebo-controlled manner. The advantage of this approach is that it would not matter whether the patients were experiencing bronchoconstriction that could be objectively measured with a spirometer or if they experienced mood changes that they rated subjectively on a scale. The findings would be equally valid.

The EMU is the only clear pathway for cracking the key conundrum, that is, whether the condition is toxigenic, psychogenic, or both, or different things in different people? This is the question that doctors and policy makers most urgently need answered. Until it is answered, the patients will remain in limbo. There is an ancient Chinese saying—"When you don't know where you're going, any road will take you there." The problem is that it may take decades to get there, especially when research funds are constrained by the very paradigmatic controversy they are needed to settle.

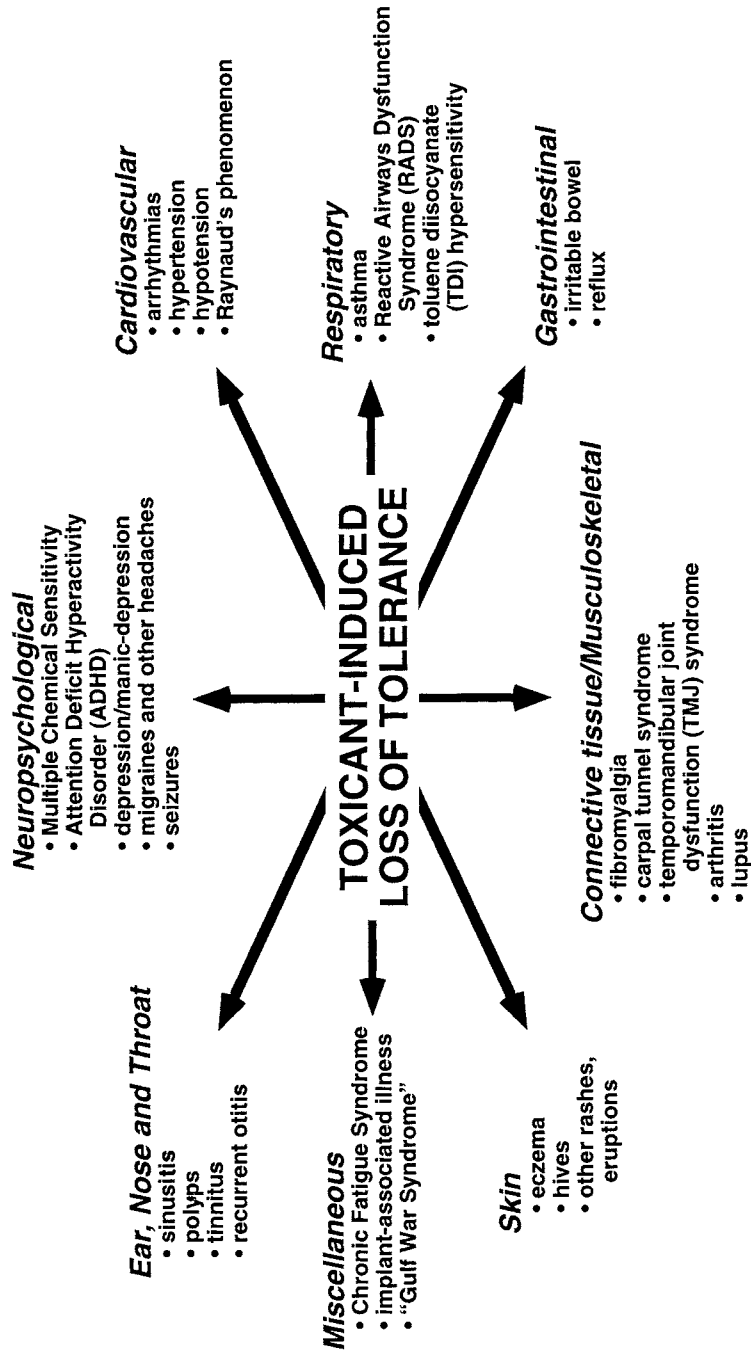


FIGURE 3. Conditions that may have their origins in TILT.

There is nothing wrong with thoughtfully contemplating potential mechanisms that might underlie this illness. However, at the same time, we need to move forward by performing the “crucial experiment”—in this case, human challenge studies in an environmentally controlled hospital unit. Kuhn³⁴ defined crucial experiments as those able to discriminate sharply between competing paradigms. The EMU experiment has the potential to do just that and will help set medicine and public health on the proper path.

Any theory that is proposed for chemical intolerance:

- Must make sense (“... the first duty of a hypothesis is to be intelligible”—Huxley).
- May be neither simple nor practical (“Make things as simple as possible, but no simpler”—Einstein).
- May require new tools to prove (the microscope allowed us to see germs; an EMU may be necessary to “see” this problem).
- May be unpopular (Copernicus showing that the Earth was not the center of the universe).
- Must be aesthetic, that is, fit existing data and allow prediction; any successful theory must be able to explain all of the salient observations, not just some of them.
- May initially seem strange and implausible (e.g., Einstein’s curved space; “What is plausible depends upon the biological knowledge of the time”—Hill).
- May transform neighboring sciences.

Chemical intolerance is no ordinary scientific anomaly. It is a “crisis-provoking” one.³⁴ As such, it has the potential to transform the fields of environmental health, medicine, psychiatry, psychology, addiction, and toxicology.

The inertia inherent in established paradigms is enormous. Even when the crucial experiment is complete, there are those who will remain skeptical. This is to be expected. Scientific revolutions proceed glacially, but inevitably. The natural history of new paradigms is known: “A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it” (Max Planck, *Scientific Autobiography*).

BIOSKETCH

Claudia S. Miller, M.D., M.S., is an Associate Professor in Environmental and Occupational Medicine in the Department of Family Practice of the University of Texas Health Science Center at San Antonio. She is board-certified in Allergy/Immunology and Internal Medicine, and has a master’s degree in Public Health/Environmental Health. Her research interests include the health effects of low-level chemical exposures, pesticides, indoor air pollution, and Gulf War veterans’ illnesses. She has held appointments to several federal advisory committees, including the National Advisory Committee on Occupational Safety and Health, the National Tox-

icology Program Board of Scientific Counselors, and the Department of Veterans Affairs Persian Gulf Expert Scientific Advisory Committee. She is coauthor of the WHO-award-winning *New Jersey Report on Chemical Sensitivity* and a professionally acclaimed book, *Chemical Exposures: Low Levels and High Stakes*.¹⁰

REFERENCES

1. MILLER, C. 1994. White paper: chemical sensitivity—history and phenomenology. *Toxicol. Ind. Health* **10**(4/5): 253–276.
2. MILLER, C. & T. PRIHODA. 1999. The Environmental Exposure and Sensitivity Inventory (EESI): a standardized approach for measuring chemical intolerances for research and clinical applications. *Toxicol. Ind. Health* **15**: 370–385.
3. MILLER, C. & T. PRIHODA. 1999. A controlled comparison of symptoms and chemical intolerances reported by Gulf War veterans, implant recipients, and persons with multiple chemical sensitivity. *Toxicol. Ind. Health* **15**: 386–397.
4. LAX, M. & P. HENNEBERGER. 1995. Patients with multiple chemical sensitivities in an occupational health clinic: presentation and follow-up. *Arch. Environ. Health* **50**(6): 425–431.
5. JOHNSON, A. 1996. MCS Information Exchange. Brunswick, ME.
6. MILLER, C. 1996. Chemical sensitivity: symptom, syndrome, or mechanism for disease? *Toxicology* **11**: 69–86.
7. MILLER, C. 1997. Toxicant-induced loss of tolerance: an emerging theory of disease? *Environ. Health Perspect.* **105**(suppl. 2): 445–453.
8. FIEDLER, N. & H. KIPEN. 1997. Chemical sensitivity: the scientific literature. *Environ. Health Perspect.* **105**(suppl. 2): 409–415.
9. SIMON, G., W. KATON & P. SPARKS. 1990. Allergic to life: psychological factors in environmental illness. *Am. J. Psychiatry* **147**: 901–906.
10. ASHFORD, N. & C. MILLER. 1998. *Chemical Exposures: Low Levels and High Stakes*. Wiley, New York.
11. MILLER, C. & H. MITZEL. 1995. Chemical sensitivity attributed to pesticide exposure versus remodeling. *Arch. Environ. Health* **50**(2): 119–129.
12. BLACK, D., A. RATHE & R. GOLDSTEIN. 1990. Environmental illness: a controlled study of 26 subjects with “20th Century Disease”. *J. Am. Med. Assoc.* **264**: 3166–3170.
13. KRUEZTER, R., R. NEUTRA & N. LASHUAY. 1999. Prevalence of people reporting sensitivities to chemicals in a population-based survey. *Am. J. Epidemiol.* **150**(1): 1–12.
14. FIEDLER, N., C. MACCIA & H. KIPEN. 1992. Evaluation of chemically sensitive patients. *J. Occup. Med.* **34**: 529–538.
15. DAVIDOFF, A. & L. FOGARTY. 1994. Psychogenic origins of multiple chemical sensitivity syndrome: a critical review of the research literature. *Arch. Environ. Health* **49**(5): 316–325.
16. CHESTER, A. & P. LEVINE. 1994. Concurrent sick building syndrome and chronic fatigue syndrome: epidemic neuromyasthenia revisited. *Clin. Infect. Dis.* **18**(suppl. 1): S43–S48.
17. BUCHWALD, D. & D. GARRITY. 1994. Comparison of patients with chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivities. *Arch. Intern. Med.* **154**: 2049–2053.
18. SCHIMMELPFENNIG, W. 1994. Zur problematik der begutachtung umweltbedingter toxischer gesundheitsschäden. *Bundesgesundheitsblatt* **37**: 377.
19. SARTIN, J. 1993. Infectious diseases during the Civil War: the triumph of the “Third Army”. *Clin. Infect. Dis.* **16**: 580–584.
20. GOLOMB, B.A. 1999. Pyridostigmine bromide: review of the scientific literature as it pertains to Gulf War illnesses. Volume 2. RAND. Santa Monica, CA.
21. NEWLIN, D. 1997. A behavior-genetic approach to multiple chemical sensitivity. *Environ. Health Perspect.* **105**(suppl. 2): 505–508.

22. MILLER, C. 1999. Are we on the threshold of a new theory of disease? Toxicant-induced loss of tolerance and its relationship to addiction and abidction. *Toxicol. Ind. Health* **15**: 284–294.
23. MILLER, C., N. ASHFORD, R. DOTY *et al.* 1997. Empirical approaches for the investigation of toxicant-induced loss of tolerance. *Environ. Health Perspect.* **105**(suppl. 2): 515–519.
24. BARTHA, L., W. BAUMZWEIGER, D. BUSCHER *et al.* 1999. Multiple chemical sensitivity: a 1999 consensus. *Arch. Environ. Health* **54**(3): 147–149.
25. NETHERCOTT, J., L. DAVIDOFF, B. CURBOW *et al.* 1993. Multiple chemical sensitivities syndrome: toward a working case definition. *Arch. Environ. Health* **48**: 19–26.
26. ASHFORD, N. 1995. Letter to the editor. *Am. J. Ind. Med.* **28**: 611–612.
27. GENTON, M. 1998. Shedding light on darkroom disease: progress and challenges in understanding radiology workers' occupational illness. *Can. J. Med. Radiat. Technol.* **2**(2): 60–66.
28. HIRZY, J. & R. MORRISON. 1989. Carpet/4-phenylcyclohexene toxicity: the EPA headquarters case. Presented at the Annual Meeting of the Society for Risk Analysis, San Francisco.
29. EPA (ENVIRONMENTAL PROTECTION AGENCY). 1989. Report to Congress on Indoor Air Quality. Volume II: Assessment and Control of Indoor Air Pollution.
30. ASHFORD, N., B. HEINZOW, K. LÜTIEN *et al.* 1995. Chemical Sensitivity in Selected European Countries: An Exploratory Study. A Report to the European Commission. Ergonomia. Athens, Greece.
31. MONK, J. 1996. Farmers fight chemical war. *Chem. Ind.* **February**: 108.
32. STEPHENS, R., A. SPURGEON, I. CALVERT *et al.* 1995. Neuropsychological effect of long-term exposure to organophosphates in sheep dip. *Lancet* **345**: 1135–1139.
33. CONE, J. & T. SULT. 1992. Acquired intolerance to solvents following pesticide/solvent exposure in a building: a new group of workers at risk for multiple chemical sensitivity. *Toxicol. Ind. Health* **8**(4): 29–39.
34. KUHN, T. 1970. *The Structure of Scientific Revolutions*. University of Chicago Press. Chicago.
35. OVERSTREET, D., C. MILLER, D. JANOWSKY *et al.* 1996. Potential animal model of multiple chemical sensitivity with cholinergic supersensitivity. *Toxicology* **111**: 119–134.
36. SORG, B. 1996. Proposed animal model for multiple chemical sensitivity in studies with formalin. *Toxicology* **111**: 135–145.
37. ROGERS, W., C. MILLER & L. BUNEGIN. 1999. A rat model of neurobehavioral sensitization to toluene. *Environ. Health Perspect.* **152**: 356–369.
38. ROBACK, G., L. RANDOLPH, B. SEIDMAN *et al.* 1994. *Physician Characteristics and Distribution in the United States*. American Medical Association. Chicago.
39. STATISTICAL ABSTRACTS OF THE UNITED STATES. 1994. Bernan Press. Lanham, MD.

Appendix

THE QEESI[®]

The Quick Environmental Exposure and Sensitivity Inventory (QEESI[®]) was developed as a screening questionnaire for multiple chemical intolerances (MCI) (see FIG. A1). The instrument has four scales: symptom severity, chemical intolerances, other intolerances, and life impact. Each scale contains 10 items, scored from 0 = “not a problem” to 10 = “severe or disabling problem”. A 10-item masking index gauges ongoing exposures that may affect individuals' awareness of their intolerances as well as the intensity of their responses to environmental exposures. Potential uses for the QEESI[®] include the following:

QUICK ENVIRONMENTAL EXPOSURE AND SENSITIVITY INVENTORY V-1 (QEESI)[®]

The purpose of this questionnaire is to help identify health problems you may be having and to understand your responses to various exposures. If your health problems began suddenly or became much worse after a particular exposure event, such as a pesticide exposure or moving to a new home or office building, complete pages 1-3 describing how you are now, then go back through these same questions a second time, and identify how you were before the exposure event. After you have completed all of the items on pages 1-5, fill in the "target" diagram below.

SYMPTOM STAR

Instructions: After completing pages 1 through 5, unfold page 3 so that it lies just to the right of this page. Place a small dot on the corresponding spoke for each symptom item on page 3. Connect these points. For "before and after" scores (described above), use two different colors.

CHEMICAL EXPOSURES

The following items ask about your responses to various odors or chemical exposures. Please indicate whether or not these odors or exposures would make you feel sick, for example, you would get a headache, have difficulty thinking, feel weak, have trouble breathing, get an upset stomach, feel dizzy, or something like that. For any exposure that makes you feel sick, on a 0-10 scale rate the severity of your symptoms with that exposure. For exposures that do not bother you, answer "0". Do not leave any items blank.

0 = not at all a problem
5 = moderate symptoms
10 = disabling symptoms

For each item, circle one number only:

1. Diesel or gas engine exhaust	0 1 2 3 4 5 6 7 8 9 10
2. Tobacco smoke	0 1 2 3 4 5 6 7 8 9 10
3. Insecticide	0 1 2 3 4 5 6 7 8 9 10
4. Gasoline, for example at a service station while filling the gas tank	0 1 2 3 4 5 6 7 8 9 10
5. Paint or paint thinner	0 1 2 3 4 5 6 7 8 9 10
6. Cleaning products such as disinfectants, bleach, bathroom cleaners or floor cleaners	0 1 2 3 4 5 6 7 8 9 10
7. Certain perfumes, air fresheners or other fragrances	0 1 2 3 4 5 6 7 8 9 10
8. Fresh tar or asphalt	0 1 2 3 4 5 6 7 8 9 10
9. Nailpolish, nailpolish remover, or hairspray	0 1 2 3 4 5 6 7 8 9 10
10. New furnishings such as new carpeting, a new soft plastic shower curtain or the interior of a new car.	0 1 2 3 4 5 6 7 8 9 10

Total Chemical Intolerance Score (0-100):

Name any additional chemical exposures that make you feel ill and score them from 0 to 10:

OTHER EXPOSURES

The following items ask about your responses to a variety of other exposures. As before, please indicate whether these exposures would make you feel sick. Rate the severity of your symptoms on a 0-10 scale. Do not leave any items blank.

0 = not at all a problem
5 = moderate symptoms
10 = disabling symptoms

For each item, circle one number only:

1. Chlorinated tap water	0 1 2 3 4 5 6 7 8 9 10
2. Particular foods, such as candy, pizza, milk, fatty foods, meats, barbecue, onions, garlic, spicy foods, or food additives such as MSG	0 1 2 3 4 5 6 7 8 9 10
3. Unusual cravings, or eating any foods as though you were addicted to them; or feeling ill if you miss a meal	0 1 2 3 4 5 6 7 8 9 10
4. Feeling ill after meals	0 1 2 3 4 5 6 7 8 9 10
5. Caffeine, such as coffee, tea, Snapple, cola drinks, Big Red, Dr. Pepper or Mountain Dew, or chocolate	0 1 2 3 4 5 6 7 8 9 10
6. Feeling ill if you drink or eat less than your usual amount of coffee, tea, caffeinated soda or chocolate, or miss it altogether	0 1 2 3 4 5 6 7 8 9 10
7. Alcoholic beverages in small amounts such as one beer or a glass of wine	0 1 2 3 4 5 6 7 8 9 10
8. Fabrica, metal jewelry, creams, cosmetics, or other items that touch your skin	0 1 2 3 4 5 6 7 8 9 10
9. Being unable to tolerate or having adverse or allergic reactions to any drugs or medications (such as antibiotics, anesthetics, pain relievers, x-ray contrast dye, vaccines or birth control pills), or to an implant, prosthesis, contraceptive chemical or device, or other medical, surgical or dental material or procedure	0 1 2 3 4 5 6 7 8 9 10
10. Problems with any classical allergic reactions (asthma, nasal symptoms, hives, angioedema or eczema) when exposed to allergens such as: tree, grass or weed pollen, dust, mold, animal dander, insect stings or particular foods	0 1 2 3 4 5 6 7 8 9 10

Total Other Intolerance Score (0-100):

FIGURE A1. The QEESI[®] questionnaire.

SYMPTOMS		MASKING INDEX		IMPACT OF SENSITIVITIES	
<p>The following questions ask about symptoms you may have experienced commonly. Rate the severity of your symptoms on a 0-10 scale. Do not leave any items blank.</p> <p>0 = not at all a problem 3 = moderate symptoms 10 = disabling symptoms</p>					
1	Problems with your muscles or joints, such as aching, cramping, stiffness or weakness?	NO	YES-1	1. Your diet	0 1 2 3 4 5 6 7 8 9 10
2	Problems with burning or irritation of your eyes, or problems with your skin, such as itching, dryness, or a lot of mucus, post-nasal drainage, or respiratory infections?	NO-0	YES-1	2. Do you drink any alcoholic beverages, beer, or wine once a week or more often?	0 1 2 3 4 5 6 7 8 9 10
3	Problems with your heart or chest, such as irregular heart rate, skipped beats, or heart pounding, or chest discomfort?	NO-0	YES-1	3. Do you consume any caffeinated beverages once a week or more often?	0 1 2 3 4 5 6 7 8 9 10
4	Problems with your stomach or digestive tract, such as abdominal pain or cramping, bloating, constipation, or diarrhea, or constipation?	NO-0	YES-1	4. Do you routinely (once a week or more) use perfume, hairspray, or other scented personal care products?	0 1 2 3 4 5 6 7 8 9 10
5	Problems with your ability to think, such as difficulty concentrating or remembering things, or having trouble making decisions?	NO-0	YES-1	5. Has either your home or your workplace been sprayed for insects or fumigated in the past year?	0 1 2 3 4 5 6 7 8 9 10
6	Problems with your mood, such as feeling tense or nervous, irritable, or sad, or having spells of crying or crying spells, or things that used to interest you?	NO-0	YES-1	6. In your current job or hobby, are you routinely (once a week or more) exposed to any chemicals, smoke or fumes?	0 1 2 3 4 5 6 7 8 9 10
7	Problems with balance or coordination, or dizziness, or with focusing your eyes?	NO-0	YES-1	7. Other than yourself, does anyone routinely smoke inside your home?	0 1 2 3 4 5 6 7 8 9 10
8	Problems with your head, such as headaches or a feeling of pressure or fullness in your face or head?	NO-0	YES-1	8. Is either a gas or propane stove used for cooking in your home?	0 1 2 3 4 5 6 7 8 9 10
9	Problems with your skin, such as a rash, hives or dry skin?	NO-0	YES-1	9. Is a scented fabric softener (liquid or dryer sheet) routinely used in laundering your clothes or bedding?	0 1 2 3 4 5 6 7 8 9 10
10	Problems with your urinary tract or genitals, such as pelvic pain or frequent or urgent urination? (For women: or discomfort or other problems with your menstrual period?)	NO-0	YES-1	10. Do you routinely (once a week or more) take any of the following: steroid pills, such as prednisone; pain medications requiring a prescription; medications for depression, anxiety, or mood disorders; medications for sleep; or recreational or street drugs?	0 1 2 3 4 5 6 7 8 9 10
Total Symptom Score (0-100):		Masking Index (0-10):		Total Life Impact Score (0-100):	
[]		[]		[]	

FIGURE A1. The QEESI[®] questionnaire — continued.

For additional copies of the QEESI, call 210-567-7760. For more information about this questionnaire, refer to Chemical Exposures: Low Levels and High Stakes (2nd Edition) by Nicholas A. Ashford and Claudia S. Miller, John Wiley & Sons, Inc., 1998. To order, call toll-free 1-800-225-5545.

UTHSCSA © 1998

- (1) Research—to characterize and compare study populations and to select subjects and controls.
- (2) Clinical evaluations—to obtain a profile of patients' self-reported symptoms and intolerances. The QEESI[®] can be administered at intervals to follow symptoms over time or to document responses to treatment or exposure avoidance.
- (3) Workplace or community investigations—to identify and assist those who may be more chemically susceptible or who report new intolerances. Affected individuals should have the option of discussing results with investigators or their personal physicians.

Individuals whose symptoms began or intensified following a particular exposure event can fill out the QEESI[®] using two different ink colors, one showing how they were before the event and the second how they have been since the event. On the cover of the QEESI[®] is a "Symptom Star" (FIG. A2), which provides a graphical representation of patients' responses on the symptom severity scale.

For additional copies of the QEESI[®], contact Claudia S. Miller at the address given on page 1 of this article. For further information, see *Chemical Exposures: Low Levels and High Stakes* by Ashford and Miller [1998, Wiley (1-800-225-5945)].

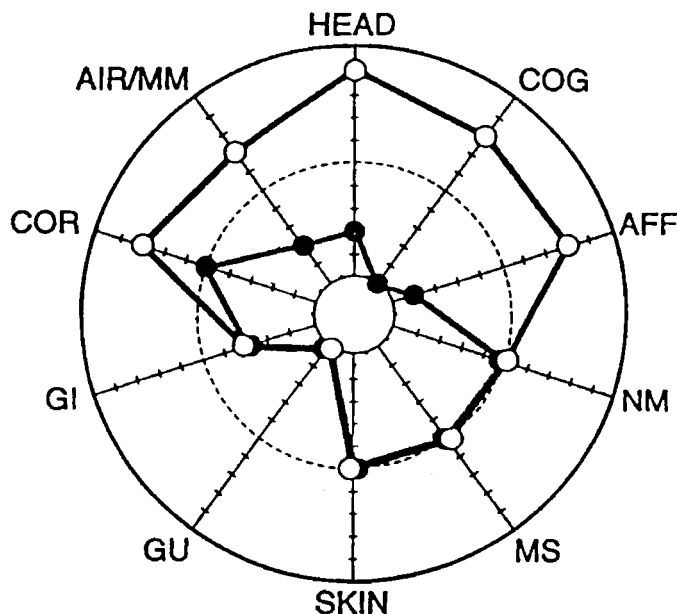


FIGURE A2. QEESI[®] Symptom Star illustrating symptom severity in an individual before and after an exposure event (e.g., pesticide application, indoor air contaminants, chemical spill). Terms: HEAD = head-related symptoms; COG = cognitive symptoms; AFF = affective symptoms; NM = neuromuscular symptoms; MS = musculoskeletal symptoms; SKIN = skin-related symptoms; GU = genitourinary symptoms; GI = gastrointestinal symptoms; COR = heart/chest-related symptoms; AIR/MM = airway or mucous membrane symptoms; (●) before exposure event; (○) after exposure event.

TABLE A1. Criteria for low, medium, and high scale scores

Scale/Index	Score		
	Low	Medium	High
Symptom severity	0–19	20–39	40–100
Chemical intolerance	0–19	20–39	40–100
Other intolerance	0–11	12–24	25–100
Life impact	0–11	12–23	24–100
Masking index	0–3	4–5	6–10

TABLE A2. Distribution of subjects by group using “high” cutoff points for symptom severity (≥ 40) and chemical intolerances (≥ 40), with masking low or not low (< 4 or ≥ 4)

Degree to which MCI is suggested ^b	Risk criteria ^a			Percentage of each group meeting risk criteria				
	Symptom severity score	Chemical intolerance score	Masking score	Controls (n = 76)	MCS: no event (n = 90)	MCS: event (n = 96)	Implant (n = 87)	Gulf War veterans (n = 72)
Very suggestive	≥ 40	≥ 40	≥ 4	7	16	23	39	45
Very suggestive	≥ 40	≥ 40	< 4	0	65	66	36	4
Somewhat suggestive	≥ 40	< 40	≥ 4	3	1	2	16	26
Not suggestive	≥ 40	< 40	< 4	0	0	2	3	6
Problematic	< 40	≥ 40	≥ 4	7	3	1	1	0
Problematic	< 40	≥ 40	< 4	3	13	4	2	0
Not suggestive	< 40	< 40	≥ 4	68	1	0	2	18
Not suggestive	< 40	< 40	< 4	12	1	2	1	1
				100	100	100	100	100

^aSubjects must meet all three criteria, that is, symptom severity, chemical intolerance, and masking scores, as indicated in each row of this table.

^bTerms: “very suggestive” = high symptom and chemical intolerance scores; “somewhat suggestive” = high symptom score, but possibly masked chemical intolerance; “not suggestive” = either (1) high symptom score, but low chemical intolerance score with low masking, or (2) low symptom and chemical intolerance scores; “problematic” = low symptom score, but high chemical intolerance score. Persons in this category with low masking (< 4) may be sensitive individuals who have been avoiding chemical exposures for an extended period (months or years).

INTERPRETING THE QEESI[®]

In a study of 421 individuals, including four exposure groups and a control group, the QEESI[®] provided sensitivity of 92% and specificity of 95% in differentiating between persons with MCI and the general population.^{1,2}

Cronbach’s alpha reliability coefficients for the QEESI[®]’s four scales—symptom severity, chemical intolerances, other intolerances, and life impact—were high (0.76–0.97) for each of the groups, as well as over all subjects, indicating that the questions on the QEESI[®] form scales showing good internal consistency. Pearson

correlations for each of the four scales with validity items of interest, that is, life quality, health status, energy level, body pain, ability to work, and employment status, were all significant and in the expected direction, thus supporting good construct validity.

Information on the development of this instrument, its interpretation, and results for several populations have been published.^{1,2} Proposed ranges for the QEESI[®]'s scales and guidelines for their interpretation appear in TABLES A1 and A2.

REFERENCES

1. MILLER, C. & T. PRIHODA. 1999. The Environmental Exposure and Sensitivity Inventory (EESI): a standardized approach for measuring chemical intolerances for research and clinical applications. *Toxicol. Ind. Health* **15**: 370–385.
2. MILLER, C. & T. PRIHODA. 1999. A controlled comparison of symptoms and chemical intolerances reported by Gulf War veterans, implant recipients, and persons with multiple chemical sensitivity. *Toxicol. Ind. Health* **15**: 386–397.