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Multiple Chemical Intolerance

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I. BACKGROUND

From time to time, physicians encounter patients with a chief complaint of hyperosmia accompanied by multisystem symptoms and intolerances for a wide variety of chemicals, foods, and/or drugs (Ashford and Miller, 1998; Berglund et al., 1992; Doty et al., 1998). Often these patients say they become ill when exposed to various odors, often in response to cacosmia (Ryan et al., 1988) or dysosmia (Miller, 1996). For example, they may describe everyday exposures to fragrances, diesel exhaust, new plastic car interiors, household cleaners, etc. (Table 1), as being overpowering, "stronger than ever before," or "extremely irritating" and triggering symptoms such as headaches, fatigue, memory difficulties, mental confusion, anxiety, irritability, depression, myalgias, arrhythmias, dyspnea, and every sort of gastrointestinal problem (Table 2). This clinical presentation has come to be known as multiple chemical sensitivity (MCS) or multiple chemical intolerance. Patients presenting with this peculiar combination of subjective hyperosmia, multisystem symptoms, and multiple intolerances appear to be on the increase (AOEC, 1992; NIEHS, 1997; NRC, 1992). Later in this chapter, epidemiological and clinical studies of this phenomenon will be reviewed.

Several things are puzzling about these patients. First, the levels of chemicals they say trigger their symptoms are orders of magnitude below established safety limits, leading some physicians to dismiss the illness on the basis that it violates a fundamental tenet of toxicology—evidence of a dose-response relationship (Waddell, 1993). Second, the substances these patients implicate are *structurally unrelated*, an observation unsettling for toxicologists and immunologists, who tend to think of receptors, biochemical pathways, and target organs as being substance- or at least class-specific.

Third, these patients report a baffling array of symptoms involving any and every organ system, and often several systems simultaneously. Fourth, the vast majority of patients attest that chemical odors and even nonodorous chemical exposures trigger cognitive difficulties and mood disturbances, symptoms physicians tend to see as psychogenic. The fact that these patients' symptoms overlap with those of chronic fatigue syndrome, somatoform disorder, fibromyalgia, panic disorder, and posttraumatic stress disorder adds to the confusion.

Despite the phenomenon's seeming implausibility, in recent years similar patterns of multisystem symptoms and multiple chemical, food, and drug intolerances have surfaced in more than a dozen countries (nine European nations, the United States, Canada, Japan, Australia, New Zealand) among demographically diverse groups—groups having little in common, save some initial chemical exposure event (Ashford and Miller, 1998). Among these groups are radiology workers in New Zealand exposed to x-ray developer solutions containing glutaraldehyde (Genton, 1998), EPA employees in the agency's Washington, D.C., headquarters exposed to airborne organic chemicals arising from construction, painting, and new carpeting (Hirzy and Morison, 1989), families in Germany exposed to pentachlorophenol used to preserve log homes (Ashford et al., 1995), sheep dip-

Table 1 Triggering Exposures Reported by 80% or More of Persons with Chemical Intolerances That Developed Following an Exposure to Pesticides ($n=37$) or Indoor Air Contaminants ($n=75$)

New carpeting	Enclosed mall
New automobile interior	Oil-based paint
Poorly ventilated meeting rooms	Particle board
Perfume	Gas engine exhaust
Detergent aisle in grocery	Hotel rooms
Newspaper/printed materials	Phenolic disinfectants
Fresh asphalt/tar	Dry-cleaned clothes
Diesel exhaust	Insecticides
Felt-tip markers	Gasoline
Nail polish/remover	Potpourri
Restroom deodorizers	New tires
Fabric stores	Cigar smoke
Heavy traffic	Cigarette smoke
New plastic shower curtain	Incense
Hairspray	Insect repellent

Source: Miller and Mitzel, 1995.

pers in Great Britain exposed to organophosphate pesticides (Ashford and Miller, 1998; Monk, 1996; Stephens et al., 1995), hospital workers in Nova Scotia exposed to building air contaminants (Ashford and Miller, 1998), casino card dealers in Lake Tahoe, California, exposed to solvents and pesticides (Cone and Sult, 1992), breast and temporomandibular joint implant recipients (Miller and Prihoda, 1999a,b), and Gulf War veterans exposed to solvents, smoke, fuels, pesticides, and various drugs (Bell et al., 1998, Fiedler et al., 1996b; Miller and Prihoda, 1999a,b).

What has attracted scientific attention to this problem is the fact that such diverse groups—people from different occupations, socioeconomic classes, countries and cultures, people who do not see the same doctors, watch the same television shows, or read the same books—are presenting with such similar patterns of multisystem symptoms and new-onset intolerances preceded by an initial chemical exposure event. The fact that the new-onset intolerances these patients report include medications, foods, alcohol, and caffeine—not just chemical inhalants—makes these worldwide observations compelling. Some scientists regard this repeating pattern as early evidence of an emerging new paradigm or theory of disease, one with the potential to explain a broad spectrum of illnesses including certain cases of asthma, migraine headaches, and depression, as well as chronic fatigue syndrome, fibromyalgia, and Gulf War syndrome.

Table 2 Symptoms Commonly Reported by Chemically Intolerant Individuals[a]

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

[a] 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 ($n = 37$).
Source: Miller and Mitzel, 1995.

A. Historical Background

In the 1950s an allergist named Theron Randolph described a cosmetic saleswoman who experienced dyspnea, asthma, fatigue, irritability, depression, and intermittent loss of consciousness whenever she smelled "man-made combustion products and derivatives of gas, oil, and coal" (Randolph, 1962; Randolph and Moss, 1980). Randolph coined the term "chemical susceptibility" to describe her condition. Subsequently, other physicians, seeing similar problems in their patients, allied with Randolph to found the Society for Clinical Ecology (renamed in 1984 the American Academy of Environmental Medicine). These clinicians adopted Randolph's principal diagnostic and therapeutic approach—trial avoidance of common chemicals and foods and, if patients' symptoms cleared, re-introduction of single substances one at a time to determine which, if any, triggered symptoms. Over time, some clinical ecologists adopted unorthodox diagnostic and treatment approaches, such as the administration of "neutralizing" chemical and food extracts (via injection or sublingually) and sauna "detoxification" to "sweat out" chemical contaminants, practices that drew criticism from professional medical societies (AAAAI, 1981, 1986, 1999; ACP, 1989; AMA, 1992).

Professional concerns over these and other "alternative" treatments continue. Recently, there has been a softening of positions taken against the illness as a new group of doctors—board-certified occupational and environmental medicine physicians in universities—have begun to study this phenomenon (ACOEM, 1999; Ashford and Miller, 1998). The American College of Occupational and Environmental Medicine now "supports scientific research into the phenomenon of MCS to help explain and better describe its pathophysiologic features and define appropriate clinical interventions" (ACOEM, 1999). There is widespread agreement that these patients report certain distinctive features—multisystem symptoms and multiple intolerances—whether they have seen a clinical ecologist or not (Davidoff and Keyl, 1996). In 1987, Mark Cullen at Yale University edited a compendium of papers entitled *Workers with Multiple Chemical Sensitivities: An Overview*, introducing occupational/environmental medicine practitioners to the problem (Cullen, 1987). He defined "multiple chemical sensitivity" as "an acquired disorder characterized by recurrent symptoms, referable to multiple organ systems, occurring in response to demonstrable exposure to many chemically unrelated compounds at doses far below those established in the general population to cause harmful effects. No single widely accepted test of physiologic function can be shown to correlate with symptoms."

B. Recent Developments

Over the past decade there has been an outpouring of technical reports, concept papers, and hypotheses concerning chemical intolerance. The terms "multiple chemical sensitivity" and "environmental illness" appear on the National Library of Medicine's bibliographical database, Medline. While it is generally agreed that a problem exists and that patients are suffering, medical opinion remains polarized as to whether the condition is a unitary one or a potpourri, and whether it arises from chemical exposures, psychological factors, or a blend of these. There is mounting concern that if low-level chemical exposures were found to cause this problem, the implications for environmental policy, product liability, workers' compensation, and medical treatment would be staggering.

Several nations have examined the issue, with Canada leading the way through its 1985 Thomson Report (Thomson, 1985) and sponsorship of clinical studies and scientific meetings. In the United States, the phenomenon has been explored by New Jersey, Maryland, and California (Ashford and Miller, 1989; Bascom, 1989; Kreutzer et al., 1999), various federal environmental agencies (ATSDR, 1994; Fiedler and Kipen, 1997a), the National Academy of Sciences (NRC, 1992), and professional organizations (ACS, 1999; AOEC, 1992). While promising research strategies have emerged from these meetings (summarized in Ashford and Miller, 1998), few comprehensive or illuminating studies have been funded. At this time, underlying mechanisms remain unknown, treatments are empirical, and no environmentally controlled hospital facility is available in the U.S. for clinical research, diagnosis, or treatment. Patients continue to suffer, while funding for serious scientific study is mired by the very medical debate such studies are needed to settle. Amid the confusion of opinion swirling around the illness, affected individuals and their caregivers are in need of rational, low-risk interim interventions with the potential to alleviate suffering and foster recovery. Of equal importance, there is a need to *prevent* exposures (e.g., to pesticides, chemicals associated with new construction) that could disable currently healthy, but potentially susceptible, people.

II. DEFINING THE PROBLEM

At the present time, physicians and researchers cannot agree upon a name for this condition, much less whether it is a single illness or a group of related or unrelated conditions that simply share the symptom of chemical intolerance. One thing is clear. The problems these patients report do not con-

stitute a syndrome: By definition, a syndrome is "a group of symptoms or signs typical of a disease" (Webster's, 1986). The symptoms these patients report are simply too heterogeneous to be collapsed into a single syndrome—perhaps a collection of syndromes, but not a single one.

A. Sensitivity or Intolerance?

The various meanings of the term "sensitivity" contribute to the confusion surrounding the condition(s). The word sensitivity is used in three relatively distinct ways (Ashford et al., 1995):

1. The heightened responses of certain individuals to known toxicants or allergens, i.e., the responses of people who are especially susceptible to toxic substances like mercury or carbon monoxide or to allergens like housedust mites or bee venom.
2. The responses of certain individuals to identifiable exposures which cannot be explained by disease mechanisms generally understood by doctors. This category includes: (a) sick building syndrome, involving individuals who respond adversely to one or several air contaminants which may or may not be identifiable. Evidence for sick building syndrome's existence rests on the fact that affected individuals' symptoms resolve when they leave the problem building; (b) sensitivity, such as that induced by toluene diisocyanate (TDI), which starts out as hypersensitivity to a specific chemical, or a single chemical class, but evolves into nonspecific hyperresponsiveness (further described in category 3 below).
3. The heightened, extraordinary, or unusual responses of certain individuals to structurally unrelated chemicals at exposure levels orders of magnitude below those affecting most people.

Multiple chemical sensitivity fits in this third category. Synonyms and related terms for MCS include environmental illness (EI), chemical intolerance, ecological illness, idiopathic environmental intolerance (IEI), universal allergy, and toxicant-induced loss of tolerance (TILT). A bright line needs to be drawn between MCS and antibody-mediated sensitivities or allergies. Allergists use the term "chemical intolerance" (not "chemical sensitivity") to distinguish this third category from classical allergies. The word "sensitivity" poses a problem: it implies that sensitization has occurred, when, in fact, the loss of tolerance these individuals experience might arise from something entirely different, e.g., cell membrane disruption or gene activation. So instead of "sensitization," the term "chemical intolerance" is used in this chapter. The latter presumes no particular etiology; instead, it nourishes fresh ideas and encourages new discoveries. Tolerance, as used here, is the ability to withstand an insult. Chemically intolerant individuals appear to have lost their prior natural or innate tolerance for a wide variety of chemicals, foods, and drugs.

B. Proposed Case Definitions

Despite the differing opinions and semantic difficulties in this area, several case definitions for this phenomenon have been proposed (summarized in Ashford and Miller, 1998), some of which may prove useful, e.g., for research, medical evaluation purposes, or compensation (AOEC, 1992; Bartha et al., 1999; Nethercott et al., 1993; NRC, 1992). The original Cullen case definition, used in some early studies, unfortunately excludes "diagnosable" conditions such as asthma or depression (Cullen, 1987), when in fact chemical intolerance might underlie certain cases of asthma or depression. One operational case definition calls for sick individuals to be removed from background chemical, food, and drug exposures to determine whether their symptoms clear, and, if they do, administering single, double-blinded, placebo-controlled chemical challenges to see which, if any, trigger symptoms. The latter, patient-focused approach to "defining" multiple chemical intolerance is considered the "gold standard" for the field and has emerged as a principal research recommendation from several scientific meetings (AOEC, 1992; Miller et al., 1997; NRC, 1992).

Bartha et al. (1999) offer six "consensus criteria" for multiple chemical sensitivity culled from a survey of 89 clinicians and researchers familiar with the illness but whose opinions concerning its origins differed (Nethercott et al., 1993): (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...." Patients who experience short-lived symptoms associated with a particular odor or exposure, e.g., tobacco smoke, mothballs, or paint vapors, but whose symptoms stop when the exposure ends with no recurrence or spreading to other substances should not be labeled as having multiple chemical intolerance.

III. PHENOMENOLOGY

About 50–60% of chemically intolerant individuals say their illness began following a specific chemical exposure (or a series of exposures), referred to as an initiating event, e.g., a chemical spill, repeated exposure to solvents, a pesticide application, indoor air contaminants associated with new construction, combustion products (Fiedler et al., 1996a; Miller, 1994). Only a subset of those exposed appear to develop chronic symptoms and intolerances. What makes some individuals more susceptible remains a mystery. Initially, patients may describe "flu-like" symptoms that fail to resolve, or feeling as though they are in a "perpetual fog." Next to develop are multisystem symptoms that seem to wax and wane unpredictably, followed by a dawning awareness of specific intolerances, frequently involving alcoholic beverages or medications at first. Over time, these intolerances spread to include a wide variety of everyday exposures—chemical odors (low levels of volatile compounds), foods, drugs, caffeine, alcoholic beverages, and skin contactants. Food intolerances may appear but not be recognized as such. Instead, patients may complain of digestive difficulties, feeling ill after meals, or becoming irritable if a meal is missed or delayed.

These intolerances may begin within weeks of an acute, high-level exposure or, as in the case of a sick office building, emerge insidiously over months or years. Symptoms may be triggered via any exposure route—inhalation, ingestion, injection (e.g., drugs), or skin or mucosal contact. Some patients report that breathing through their mouths instead of their noses, e.g., around traffic exhaust or people wearing fragrances, mitigates their symptoms somewhat. Particular odors or exposures (see Table 1)—whether fragrances, chemicals outgassing from new furnishings or carpeting, traffic exhaust, cleaning agents, etc.—may trigger different constellations of symptoms in different individuals. An individual patient often reports different responses with different exposures. Symptom intensity may range from mild (e.g., nasal congestion, nausea, or slight headache) to severe (e.g., mental confusion, depression or seizures) (Table 2). There is consistency, however: a particular exposure, e.g., diesel exhaust or a certain fragrance, in a particular person tends to elicit a characteristic constellation of symptoms, a so-called "signature response." Responses may occur at below-olfactory-threshold concentrations, with symptoms developing within seconds to hours after a triggering exposure and persisting minutes to days. Hyperresponsiveness to physical stimuli, including light, noise, and touch, is commonly reported (Miller and Prihoda, 1999 a,b). Patients may wear sunglasses indoors or dim the room to keep bright light from reaching their eyes. Although some patients report hypersensitivity to odorants, there are anecdotal reports of anosmic individuals suffering from multiple chemical intolerance.

Various studies and surveys suggest that patients who systematically avoid problem exposures find some relief (Johnson, 1996; Lax and Henneberger, 1995), but comprehensive avoidance is challenging, as well as socially isolating. Common odors involving low-level volatile organic chemicals (VOC) in the parts per billion or parts per trillion range are near-ubiquitous. Making matters worse, physicians, and even the patients themselves, may fail to discern symptom-exposure relationships (Ashford and Miller, 1998). Several factors may contribute to this. For example, habituation can occur with chronic or repeated exposure to the same substance(s), e.g., volatile organic chemicals in a sick office building. Second, apposition, i.e., overlapping symptoms resulting from various exposures (chemicals, foods, drugs), may hide or "mask" the effects of particular exposures. According to this scenario, the intolerant individual who applies hairspray and fragrances in the morning, cooks breakfast on a gas stove, and drives through heavy traffic to a sick office building may experience near-continuous symptoms (highly masked) and fail to recognize any single exposure as causal (Miller 1996, 1997). In effect, background symptom "noise" might hide any particular "signal."

"Withdrawal" symptoms reportedly develop when patients avoid problem exposures for several days, e.g., over a weekend or while on vacation. Such avoidance can be inadvertent or deliberate, e.g., a physician-recommended trial avoidance period (see Sec. V. E). Later, with reexposure, as on a Monday morning after a weekend away from work, symptoms may return "with a vengeance." Some chemically intolerant individuals quit their jobs so as to avoid coworkers' fragrances, carbonless copy paper, cleaning agents, etc. Others switch employers, occupations, and residences in search of safer surroundings.

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 seemed to spread from sick, feverish individuals to their families and neighbors. These anomalous observations paved the way for the germ theory of disease. This germ theory, so obvious to us today, enabled scientists and the public to grasp for the first time the origins of dozens of seemingly unrelated illnesses affecting every organ system. Today, we are witnessing another anomaly—a repeating pattern of illness appearing in groups of people, including Gulf War veterans, from more than a dozen countries following chemical exposures. What unites the Gulf War veterans and these civilian groups is their common experience of an initiating chemical exposure event 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-stage process—an initial chemical exposure (initiation) leading to newly acquired intolerances, with symptoms subsequently triggered by multiple common exposures (triggering)—has been referred to as toxicant-induced loss of tolerance, or "TILT" (Fig. 1).

It does not appear to matter which exposure causes the breakdown in tolerance—be it pesticides, solvents, indoor air contaminants, smoke from oil well fires, or medications. It is the aftermath of these exposures, the new-onset intolerances to various substances, that appears to perpetuate the symptoms. Four observations suggest that toxicant-induced loss of tolerance might be a new theory of chemically induced disease:

1. The appearance of the same pattern of symptoms and new-onset odor and other intolerances in demographically diverse groups worldwide following well-defined exposures to pesticides, solvents, indoor air contaminants, etc.
2. The fact that these groups' new-onset intolerances involve not only chemical inhalants, but also various foods, medications, caffeine, alcoholic beverages, and skin contactants. These observations in particular constitute what Kuhn (1970) called a "compelling" or "critical" anomaly. Just as fever is the hallmark symptom for infection, a signal that sends doctors down certain diagnostic pathways, new chemical, food, and drug intolerances are the hallmark symptom for TILT.
3. Recent animal models replicating key features of TILT (see Sec. VI).
4. The striking parallels between this phenomenon and addiction, suggesting shared neural mechanisms likely involving multiple neurotransmitter pathways (see Sec. VI).

TILT has the potential to explain certain cases of asthma, migraine headaches, and depression, as well as chronic fatigue, fibromyalgia, and Gulf War syndrome (Fig. 2). But both stages of TILT—initiation and triggering—are in need of testing. Some argue that TILT's second stage, triggering, should be studied first and that to accomplish this, a special scientific "apparatus" needs to be built—an environmentally controlled in-patient hospital unit (environmental medical unit) in which patients can reside for a week or longer, allowing them reach a "clean" exposure baseline (Miller et al, 1997; NRC, 1992). Assuming this occurs and patients' exposure-related symptoms resolve, subjects could then be exposed to various potential triggers, including caffeine, gasoline, perfume, foods, medications, and tobacco smoke, one at a time, to determine the source of their symptoms. One limitation of the TILT theory is that it may not explain every case of chemical intolerance: not every patient is able to identify an initiating event or events. An initiating event, e.g., a pesticide application, may go unnoticed. Alternatively, genetic, psychological, nutritional and other factors may underlie their intolerances.

IV. PREVALENCE

Several large surveys suggest that 15–30% of the U.S. population consider themselves "especially" or "unusually" sensitive to certain chemical odors, while approximately 2–6% claim a physician's diagnosis of "multiple chemical sensitivity," "environmental illness," or significant daily impairment from chemical exposures (Table 3) (Kreutzer et al., 1999; Meggs et al., 1996; Voorhees, 1998). In the largest of these studies, a statewide randomized telephone interview survey conducted by the California Department of Health Services, 15.9% of participants said they were "allergic or unusually sensitive to everyday chemicals," 11.9% identified two or more chemicals that made them sick, and 6.3% reported doctor-diagnosed "environmental illness" or "multiple chemical sensitivity" (Kreutzer et al., 1999). Female gender and Hispanic ethnicity were associated with greater self-reporting of sensitivity (adjusted odds ratios of 1.63 and 1.82, respectively). Neither self-reported chemical sensitivity nor doctor-diagnosed multiple chemical sensitivity was associated with employment, educational level, marital status, geographic location, or income. The similar rates seen in California, New Mexico, and North Carolina suggest that multiple chemical intolerance could be among the most prevalent, if not the most prevalent, chemically caused medical condition(s) in the United States. The California study concluded that "surprising numbers" of people believe that common chemical exposures make them sick and that "the homogeneity of responses across race-ethnicity, geography, education, and marital status is compatible with a physiological response or with widespread societal apprehensions in regard to chemical exposure" (Kreutzer et al., 1999). While the media have fanned public fears of environmental exposures, this by no means proves the problem is psychogenic. Only careful studies can settle questions concerning etiology.

More women than men have participated in clinical studies of chemical intolerance to date (4:1 female: male ratio), with an average age in the fourth decade and educational level of at least 2 years of college (Fiedler and Kipen, 1997b). In contrast, the California statewide survey cited above found a 5:3 female:male ratio in a random general population sample. Among military and industrial populations, more males report the problem, likely reflect-

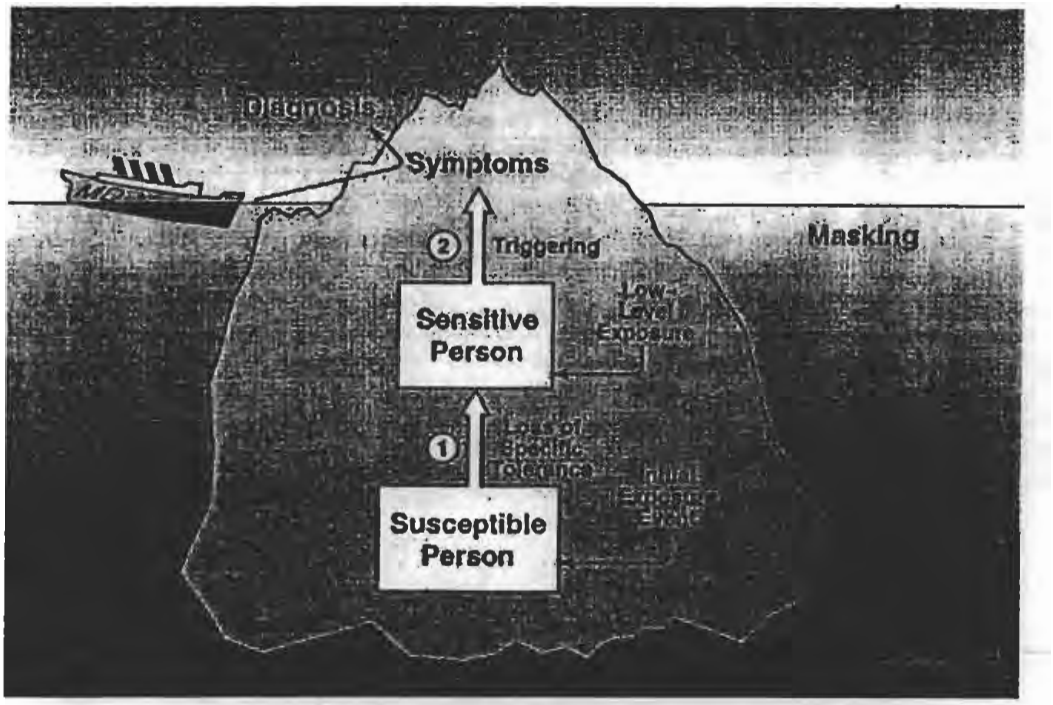

Figure 1 Phenomenology of toxicant-induced loss of tolerance (TILT). Illness appears to develop in two stages: (1) initiation, i.e., loss of prior, natural tolerance resulting from an acute or chronic exposure (pesticides, solvents, indoor air contaminants, etc.), followed by (2) triggering of symptoms 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, chronic fatigue, migraine headaches). Masking hides the relationship between symptoms and triggers. The initial exposure event causing breakdown in tolerance may also go unnoticed. (©UTHSCSA 1996.)

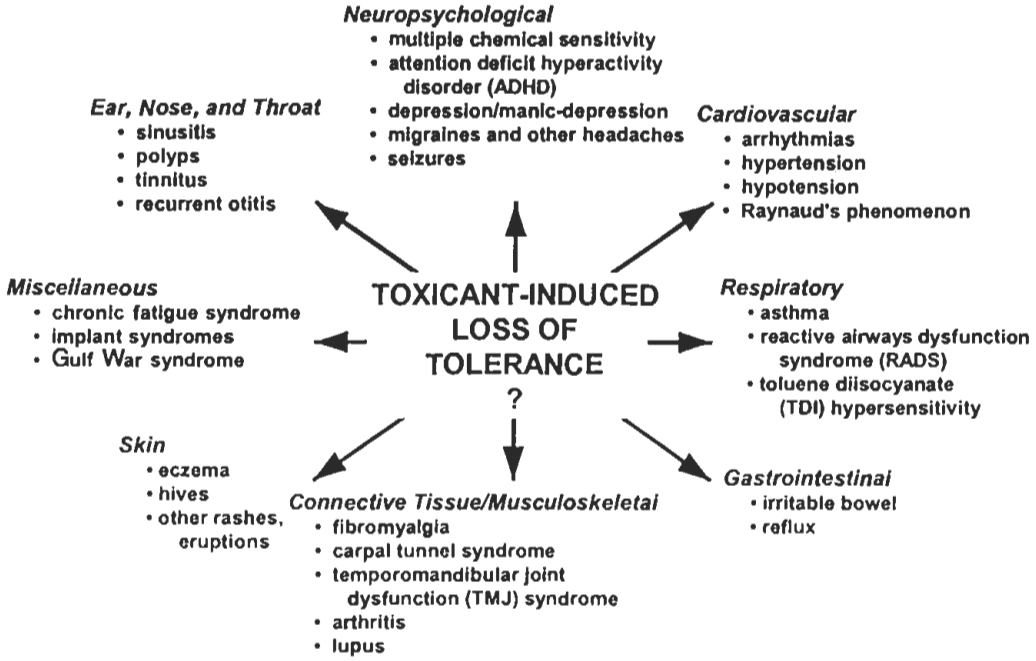

Figure 2 Conditions that may result from toxicant-induced loss of tolerance. Illnesses like depression, migraine, arthritis, and chronic fatigue may have various underlying mechanisms, one of which might be TILT.

Table 3 Frequency of Self-Reported Chemical Intolerance from Several Large Surveys

Population (Ref.)	Number of people studied	Those considering themselves especially or unusually sensitive to certain chemicals (%)	Those reporting physician-diagnosed multiple chemical intolerance or daily symptoms triggered by chemicals(%)
EPA office workers (Wallace et al., 1993)	3948	31	Not evaluated
Rural North Carolinians[a] (Meggs et al., 1996)	1027	33	3.9
California residents[a] (Kruetzer et al., 1999)	4046	15.9	6.3
New Mexico residents[a] (Voorhees, 1998)	1814	17	1.9

[a]Randomly sampled.

ing underlying gender ratios (Miller and Prihoda, 1999a,b; Simon et al., 1990;). In sick buildings, the condition is commonly reported by college-educated white females in the 30- to 50-year age range and of middle- to upper-middle-class socioeconomic status (Ashford and Miller, 1998). Why more women then men report the problem and why more chemically intolerant patients work in office buildings and service industries than in heavy industry remains unknown (Black et al., 1990; Lax and Henneberger, 1995; Miller and Mitzel, 1995;). The gender disparity may reflect women's greater willingness to report symptoms, something unique about indoor air pollutants that women may be less able to escape, e.g., as secretaries or realtors, or gender-based biological response differences. The paradox that more multiple chemical intolerance cases arise from the service sector than heavy industry may be due to (1) "the healthy worker" selection effect, i.e., individuals bothered by chemical exposures would tend to choose non-chemical jobs, (2) the fact that women, who may be biologically more vulnerable, are less apt to work in heavy industry, mining, construction, etc., or (3) some unknown but insidious effect of indoor air pollution mixtures.

Over the past decade, occupational medicine physicians have witnessed a surge in the numbers of these patients in their practices (Ashford and Miller, 1998)—another puzzle. While increased media coverage of environmental exposures has fueled our awareness, at the same time major increases have occurred in the variety and quantity of chemicals people encounter each day, all within a few generations. For example, U.S. production and use of synthetic organic chemicals have risen exponentially since World War II, rising from a billion pounds produced annually in the early 1940s to 400 billion pounds in the 1980s (U.S. International Trade Commission). And the nature of the chemicals has changed. For example, cholinesterase-inhibiting pesticides (organophosphates and carbamates) have supplanted chlorinated pesticides like DDT, on ecological grounds. The former currently account for nearly half of all pesticides used in the United States. These relatively new neurotoxic compounds, developed for agricultural use, also worked well in homes, schools, and office buildings, controlling pests with few "callbacks" for exterminators. Today, thousands of different synthetic organic chemicals are released into the air from fuels, paints, clothing, and consumer products of every description. Ninety percent of the U.S. population spends more than 90% of the day indoors, exposed to complex mixtures of volatile organic chemicals (VOCs) emitted by new carpet, pesticides, cleaners, fragrances, particle board, and furnishings. These airborne chemicals tend to accumulate in modern, sealed indoor environments. Even the air inside vehicles, especially new ones, contains myriad VOCs emitted by plastic interiors, rubber floor mats, and other components. VOCs are entrained from traffic exhaust and freshly tarred roads. Thus, the vast majority of the population is exposed near-continuously to thousands of biologically "foreign" VOCs, albeit at low levels (parts per billion or trillion).

Add to this the oil embargo of the 1970s, when U.S. home owners received tax credits for installing insulation, caulking cracks, etc., thus sealing in indoor air contaminants. Responding to the energy crunch, the American Society of Heating, Refrigeration and Air Conditioning Engineers (ASHRAE) further reduced U.S. recommendations for fresh outside air entering commercial buildings, schools, public spaces, etc., which were 30 cubic feet per minute (cfm) per occupant in 1900, down to 5 cfm per occupant—a sixfold decrease in fresh air in commercial and public buildings.* Home ventilation systems generally

* In recent years, ASHRAE fresh air requirements for public and commercial spaces have been raised to a minimum of 15 cfm per occupant, 20 cfm in offices, because of health complaints associated with the 5 cfm recommendation (ASHRAE 1999).

bring in no fresh outside air; occupants breathe only what little leaks through cracks, crevices, open doors, or windows. With more tightly sealed, "energy-efficient" structures and less fresh air brought in from outside, VOC contaminants inside homes and workplaces have crept to unprecedented levels, often orders of magnitude greater than outdoor levels. As a consequence, sick building syndrome has spread across the United States, most notoriously affecting the Environmental Protection Agency's (EPA) Washington, D.C., headquarters, where several hundred individuals fell ill following remodeling and new carpet installation (Hirzy and Morison, 1989). Several dozen EPA employees subsequently developed multiple chemical intolerances. More than a decade later, many of these individuals remain disabled (Ashford and Miller, 1998).

V. CLINICAL RECOGNITION AND EVALUATION

Physicians may be reluctant to diagnose multiple chemical intolerance even when it provides the most parsimonious description for a patient's problems. The diagnosis of multiple chemical sensitivity is frequently challenged by workers' compensation boards, employers, and others.* Some doctors opt to apply "piecemeal" but recognized and compensable diagnostic labels such as asthma, toxic encephalopathy, or migraine headache. There are no symptoms, clinical signs, or laboratory tests that are pathognomonic for multiple chemical intolerance. As for other medical conditions for which no objective diagnostic tests are available, e.g., depression, schizophrenia, and migraine headaches, health care providers must rely on careful history taking and observation over time to make the diagnosis. Circumstances permitting, patients' intolerances should be assessed through trial avoidance of suspected substances and, if improvement occurs, judicious reintroduction of single exposures under the supervision of a knowledgeable practitioner.

Where symptoms and circumstances warrant, doctors should discuss with patients the possibility of multiple chemical intolerance. Commonly reported complaints include hyperosmia, fatigue, memory and concentration difficulties, mood changes, and multisystem health problems (Table 2). Although only one organ system may be affected (especially early in the illness), multisystem involvement is the norm. The probability that the practitioner is dealing with multiple chemical intolerance rises if (1) an identifiable chemical exposure, e.g., to solvents, pesticides, combustion products, or volatile organic chemicals from a sick building, remodeling, or new construction, clearly preceded onset of the symptoms; (2) a major change in the patient's health occurred, ideally documented by increased health care utilization and/or absenteeism; (3) clinical signs or abnormal laboratory tests appear postexposure, e.g., increased liver function tests, a depressed white blood cell count, or decreased cholinesterase level; (4) new-onset depression, asthma, severe headaches, etc., appear in the absence of other clear causes; (5) others who shared the same exposure event became ill, especially but not necessarily with similar symptoms; or (6) previously tolerated chemical exposures now provoke symptoms. (7) If the patient reports newly acquired intolerances for medications, alcohol, caffeine, or foods (or feeling ill after meals), and (8) if clinical laboratory abnormalities (e.g., pulmonary function tests) improve with trial avoidance and/or worsen with reexposure, then the likelihood increases further. No one of these features "proves" the diagnosis, but the more the patient manifests, the more the practitioner should suspect toxicant-induced loss of tolerance.

Physicians need to discuss with these patients the polar opinions surrounding the illness's origins, steering them to sympathetic specialists and helping them explore treatment options, including psychological therapies and environmental interventions, while warning that all therapies currently are uproven, the underlying mechanism remains a mystery, and no test(s) are diagnostic. Much research will be needed before these patients' most pressing questions can be answered with any degree of scientific certainty. Patience on the parts of both patient and practitioner is essential. "The evaluation of a patient presenting with MCS may take several hours and it is necessary to allot sufficient time, even if inadequately reimbursed" (Sparks et al., 1994b). It is not unusual for these individuals to consult 10 or more practitioners before the problem is recognized (Miller and Mitzel, 1995). In one study, chemically intolerant patients averaged 23 health care provider visits per year (Buchwald and Garrity, 1994).

Physicians can easily underestimate the illness's multisystem impact. Chemically intolerant patients tend to migrate from specialist to specialist, accumulating diagnostic labels like toxic encephalopathy, chronic fatigue syndrome, psychosomatic illness, migraines, and fibromyalgia while remaining oblivious to the underlying dynamic. Hyperosmia, a hallmark symptom, may be overlooked in patients reporting a profusion of symptoms. Physicians'

*"Toxicant-induced loss of tolerance," which describes the breakdown in tolerance resulting from exposure—a phenomenon that has been widely witnessed by reputable scientists and reported on in numerous, peer-reviewed medical articles—has not been similarly scrutinized or challenged.

professional opinions, even when science to support them is lacking, greatly influence insurors' determinations, compensation boards, and disability reviewers, as well as employers, friends, and family. Consequently, patients tend to avoid doctors who seem skeptical or ill-informed.

A. Exposure History

Busy doctors seldom take occupational or environmental histories even when circumstances warrant (IOM, 1995). The process is time-consuming, and physicians often feel ill-equipped to interpret the information gathered. But here the value of a careful exposure history cannot be overemphasized. Standard forms for collecting basic occupational and environmental exposure information are available and should be part of every patient's chart (IOM, 1995). However, these alone are not sufficient for evaluating chemically intolerant individuals, since many common exposures (e.g., home remodeling, pesticide use) that bother these patients may be omitted from these forms. One approach is to have patients construct their own symptom/exposure time lines (one line per year), with symptoms and medical problems recorded along the top of the line and life events (e.g., changes in jobs, residences, military service, surgeries, pregnancies, remodeling, pesticide use, etc.) along the bottom. A clear, concise chronology, preferably in this format, may ferret out contributory exposures.

A standardized and validated screening questionnaire, the Quick Environmental Exposure and Sensitivity Inventory (QEESI), has been described in the medical literature and is available for evaluating these patients' symptoms and chemical/odor intolerances, monitoring their clinical course, and measuring their treatment response (Miller and Prihoda, 1999a). This 50-item inventory permits patients to rate their symptoms and intolerances before and after an exposure event. It can also help affected individuals identify potential home and workplace triggers and determine whether they may be more susceptible to various alcoholic beverages, caffeine, foods, and drugs. If intolerances to any of these preceded the alleged initiating exposure event, it may help clarify why this person, rather than others who were similarly exposed, fell ill.

Whenever possible, material safety data sheets (MSDSs) should be obtained to clarify the nature of the patients' exposures. Occupational medicine physicians, toxicologists, and industrial hygienists may help with collecting and evaluating exposure data. Occupational medicine doctors routinely take detailed exposure histories, but most do not delve into patients' food intolerances. On the other hand, allergists who are trained to evaluate food intolerances using elimination diets may be reluctant to deal with chemical exposures. Chemically intolerant patients "fall in the crack" between these two specialties.

B. Symptoms and Intolerances

Patients typically report multisystem symptoms, with fatigue being most common (Table 2). Symptoms often mimic chronic fatigue syndrome or fibromyalgia, diagnoses many patients eventually acquire (Ashford and Miller, 1998; Buchwald and Garrity, 1994; Chester and Levine, 1994; Miller and Mitzel, 1995). Mood changes, including irritability, anxiety, and depression, are commonly reported. Exposure-triggered memory and concentration difficulties have led some patients to abandon cognitively demanding careers. Affected groups report strikingly similar symptoms, whether the "initiating" event involved pesticides or construction-related indoor air contaminants (Miller and Mitzel, 1995). Central nervous system symptoms predominate. Gastrointestinal (e.g., problems digesting food), respiratory (e.g., shortness of breath or being unable to get enough air), and musculoskeletal (e.g., muscle/joint pain) problems are commonly reported (Miller and Mitzel, 1995).

Besides chemical intolerances, almost invariably these patients report responding adversely to various foods, drugs, alcoholic beverages, or caffeine. Ninety-seven percent of 112 self-reported chemically intolerant individuals in one study reported significant food intolerances, causing them to avoid their problem foods or follow elimination diets (Miller and Mitzel, 1995). Food intolerances often involve frequently eaten items and those commonly craved, e.g., bread (wheat), corn chips, chocolate, caffeinated beverages, milk, etc. Patients who experience an immediate, sharp reaction after eating a particular food tend to avoid that food, particularly if the food is unusual (e.g., avocado or cashews) and eaten only occasionally (Randolph, 1956). On the other hand, foods eaten frequently (twice weekly or more) may precipitate fatigue, headaches, mood problems, digestive difficulties, etc., but go unrecognized, due to masking. Because patients may experience a slight "pickup" shortly after these foods are eaten, they may actually crave these foods (e.g., "chocoholics"). Food-intolerant patients may insist upon having their meals on time. If they miss a meal or eat late, they may report feeling tired, jittery, achy, etc. Some snack between meals, eat just before bedtime (to avoid nighttime withdrawal symptoms or awakening), stash food by the bedside or in the car, or carry large cups of coffee or tea wherever they go, "titrating" themselves throughout the day—unconscious ploys to ward off food-withdrawal symptoms. Randolph called this phenomenon "food addiction."

Chemically intolerant individuals may report acute symptoms with minimal caffeine intake and/or caffeine withdrawal symptoms lasting a week or longer, including headaches, irritability, abdominal cramps, heart pounding, insomnia, or fatigue. Blinded, crossover studies have demonstrated that certain people who consume as little as one cup of regular coffee per day (about 100 mg of caffeine) reliably develop caffeine withdrawal symptoms when they stop (Silverman et al., 1992). Even a few sips of decaffeinated coffee (about 10 mg of caffeine per cup) are said to precipitate symptoms in some chemically intolerant patients. Initially, these individuals may consume copious quantities of caffeine in an effort to stave off withdrawal symptoms. Caffeine intolerance can be confirmed by stopping all xanthines (coffee, tea, cola, chocolate, caffeinated soft drinks) for 1–2 weeks to determine whether symptoms improve and, if improvement occurs, reintroducing caffeine while observing whether symptoms return. Withdrawal symptoms may persist 7–10 days after all xanthines are stopped. Because sudden xanthine cessation can precipitate severe withdrawal symptoms in patients prone to debilitating headaches, depression, etc., gradual tapering may be preferable in such cases, albeit withdrawal may be protracted.

Alcohol intolerance may be the first intolerance a patient notices (Miller and Prihoda, 1999a,b), perhaps because of ethanol's rapid absorption rate and the fact that most people tend to use it intermittently, often on an empty stomach. As little as one drink may precipitate acute symptoms or may be followed by several days' withdrawal symptoms (hangover). Patients rarely tell physicians they are alcohol intolerant unless the practitioner asks. Smokers may report, if queried, that smoking one more cigarette than usual or borrowing someone else's stronger brand precipitates acute symptoms such as headache, lightheadedness, shortness of breath, gagging, coughing, nervousness, or nausea. Some individuals quit or switch to lighter brands.

Patients commonly report adverse reactions to medications, for example, flu-like symptoms persisting days after methacholine challenge; becoming extremely irritable and eating ravenously after a steroid injection; chest tightness and chills following radiographic contrast dye injection; or panic attacks or floating feelings with antidepressants. Elevated liver function tests with some drugs, e.g., piroxicam, may occur. Previously well-tolerated drugs may no longer be tolerated, e.g., over-the-counter decongestants. Skin and/or systemic symptoms may occur with skin or mucosal contactants, e.g., adhesive tape, topical creams or ointments, jewelry, soaps, shampoos, plastic mouth appliances, toothpaste, contact lenses, various fabrics (wool, polyester), condoms, spermicides, cosmetics, deodorants, laundry soaps, fabric softeners, and chlorinated pool water.

C. Past Medical History and Associated Conditions

Whenever possible, past medical records should be examined, even if voluminous and difficult to obtain. A past history of unexplained illness(es) is common in this patient population. Aerospace workers who developed multiple chemical intolerances when a new composite plastic was introduced into their workplace averaged 6.2 unexplained physical symptoms preceding the change in process versus only 2.9 unexplained symptoms in unaffected coworker controls (Simon et al., 1990). Fifty-four percent of the ill workers had histories of anxiety or depression that preceded their exposure, compared with 4% of controls. Other investigators have found that past psychiatric history does not explain the illness (Fiedler et al., 1992). Even if some chemically intolerant individuals have histories of depression that predate their "initial exposure event," the question remains whether depression causes chemical intolerance, whether depressed individuals are more susceptible to chemical exposures (i.e., have vulnerable neurochemistry), or whether the earlier depression may have been due to prior, unidentified intolerances (Davidoff and Fogarty, 1994). Medical and psychiatric diagnoses reported more frequently by chemically intolerant college students include nasal allergies, hives, breast cysts, premenstrual disorder, and childhood hyperactivity (Bell et al., 1996), and among community-based chemically intolerant middle-aged individuals, rhinitis, migraines, irritable bowel, ovarian cysts, menstrual dysfunction, depression, anxiety, and panic disorder (Bell et al., 1995). Another community sample found chemically intolerant individuals more likely to seek medical help for heart problems, bronchitis, asthma, and pneumonia, and to report parental heart disease, asthma, and diabetes (Baldwin and Bell, 1998). Black et al. (1999) reported that chemically intolerant patients versus controls reported more first-degree relatives with major depression, alcoholism, panic disorder, obsessive-compulsive disorder, and antisocial personality disorder and who had made more suicide attempts and received more psychiatric treatment.

D. Physical Examination and Laboratory Evaluation

Abundant anecdotal evidence suggests that chemically intolerant individuals improve when they identify and learn to avoid exposures that trigger their symptoms. Various federally sponsored consensus groups have recommended research/diagnostic studies using an environmentally controlled, inpatient hospital unit analogous to a drug detoxification unit, in which patients could be taken to a "clean" baseline, allowing exposure-related symptoms to resolve (Fig. 3) (AOEC, 1992; Miller et al., 1997; NRC,

1992). Subjects could then be exposed to various potential triggers, including caffeine, gasoline, perfume, individual foods, medications, and tobacco smoke, one at a time, to determine what is causing their symptoms, but at this time no such facility is available in the United States.

Although a comprehensive physical examination is essential, findings frequently are unremarkable. Baseline laboratory tests such as a complete blood count and chemistry profile can be helpful, as well as tests suggested by history or physical findings, such as thyroid function tests, pulmonary function tests, peak flow monitoring over time, tests for collagen-vascular disease, and neuropsychological evaluations in some patients (Weaver, 1996). Blood tests for environmental chemicals should be used only if there is reason to suspect specific exposures, and these substances can reasonably be expected to persist in tissues (e.g., a chlorinated pesticide or recent organophosphate pesticide exposure, but not most solvent or indoor air volatile organic chemical exposures). Referrals to specialists are often necessary, given the multisystem nature of the illness and the need to rule out contributing or coexisting conditions, such as an autoimmune disease, endocrine disorder, demyelinating disease, brain tumor, etc. (Moorhead and Suruda, 2000). While specialists' evaluations can be reassuring for patients and referring physicians, unnecessary invasive testing and polypharmacy are potential pitfalls. One physician, preferably a primary care physician, needs to oversee the entire evaluation and treatment, integrating specialists' advice as appropriate.

To date, no consistently abnormal laboratory findings have been demonstrated in these patients. Various studies have reported abnormalities in T- and B-lymphocyte counts; helper/suppresser T-cell ratios; immunoglobulin levels; autoimmune antibodies (e.g., anti-nuclear, anti-smooth muscle, anti-thyroid, anti-parietal cell, etc.); activated T lymphocytes (TA1 or CD26); quantitative EEGs; evoked potentials; SPECT and other brain scans (Heuser and Mena, 1997; Hu et al., 1999; Mayberg, 1994; Rossi et al., 1999; Waxman, 2000); vitamin, mineral, amino acid, and detoxification enzyme levels; and blood or tissue levels of pesticides, solvents, and other chemicals. Common flaws in studies conducted to date include failures to (1) define the study population (no case definition used), (2) compare cases with age- and sex-matched controls, (3) blind specimens, and (4) document the test method's accuracy and reproducibility. Some illness proponents claim that different immunological abnormalities occur in different patients. However, if enough tests are done, statistically a certain number can be expected to be abnormal (e.g., 1 in 20), a fact frequently forgotten. Mitchell et al. (2000) recommend that "[p]atients should be informed that subtle differences in individual immunological parameters, especially if observed in only one laboratory, are common and do not necessarily indicate the presence of a systemic

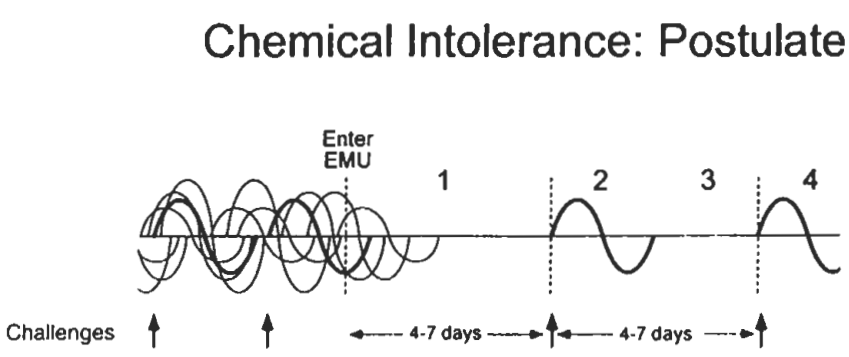

Figure 3 Use of an environmental medical unit (EMU) in the evaluation of health effects from low level chemical exposures. The figure illustrates stages in the evaluation of a patient in an EMU. At left, prior to entering the EMU, a patient is experiencing overlapping symptoms in response to everyday exposures and is unable to discern the effects of any particular exposure. Background symptom "noise" is high, and, to the patient, symptoms seem to wax and wane unpredictably over time. (1) With entry into the EMU and the avoidance of all chemical, food, and drug triggers simultaneously, remission of symptoms should begin. During the first few days of "withdrawal," irritability, headaches, and depression are expected complaints. Within a week, the individual should be at a clean baseline and ready for challenge testing. (2) Following a chemical, food, or drug challenge (arrows), the patient should report a specific constellation of symptoms. (3) When the challenge ends, patients should gradually return to baseline and be free of symptoms. If the individual is re-challenged with the same substance 4 to 7 days after the first challenge, the same constellation of symptoms should occur. Challenges involving unrelated chemicals or foods may take place in the interim.

disorder, unless there are additional clinical correlates and the results are verified."

E. Trial of Avoidance

There are anecdotal reports of patients diagnosed with this condition early in its course who avoided further exposure and apparently recovered (Hileman, 1991), suggesting that timely recognition and avoidance might reverse the illness and prevent disability. Our current inability to treat the condition once entrenched underscores the importance of early intervention. Physicians need to recognize patients who may be in the initiation phase of the illness and who may have ongoing exposures to pesticides, remodeling, solvents, etc. These individuals may benefit from a period of trial avoidance to determine whether they improve, followed by judicious, medically supervised reexposure to determine whether their symptoms recur. Unfortunately, at this time most patients are diagnosed long after their illness begins.

Almost uniformly, patients report that identifying and avoiding chemical and food triggers benefit them most (Lax and Henneberger, 1995). While conceptually simple, avoiding potential incitants is no simple task, particularly for patients with cognitive difficulties. As a rule, patients need help identifying and minimizing exposures to volatile organic chemicals released by fragrances, cleaners, and other products. Simply telling them to avoid exposures that trigger their symptoms is not sufficient. Initially, they may be loathe to relinquish their favorite fragrances, soaps, candles, gas stoves, foods, etc., even on a trial basis.

Because avoidance of alcoholic beverages, nicotine, caffeine, medications, and problem foods can precipitate severe withdrawal symptoms in susceptible individuals, e.g., severe headaches, disorientation, depression, and malaise, such regimens should not be attempted on an outpatient basis unless supervised by a knowledgeable medical practitioner. Patients with histories of severe asthma, headaches, depression, or other medical conditions (especially if emergency management was ever required) should be hospitalized in an environmentally controlled medical unit during the initial stages of avoidance.

The vast majority of patients find that avoiding problem foods makes them feel better (Johnson, 1996; LeRoy et al., 1996; Miller and Mitzel, 1995). Various elimination diets have been used with these patients, most often the rotary diversified elimination diet, in which no food or food group is consumed more than once every 4 days (Rinkel, 1944; Rinkel et al., 1951). Popular versions of this diet have appeared (Mandell and Scanlon, 1979). Adhering to restrictive diets is difficult, and research is needed to determine their efficacy. However, modifying patients' timing of food intake in order to uncover possible food intolerances is relatively innocuous, provided nutrition is maintained. If multiple food intolerances are found, achieving adequate nutrition may be difficult. Long-standing digestive difficulties and/or use of restrictive diets can result in nutrient deficiencies.

It may be helpful to have patients maintain a daily log or diary (one page per day), recording each symptom (scored on a 0–10 intensity scale) and listing all inhalant and ingestant exposures and the times at which exposures and symptoms occurred. Review of this log may help reveal problem exposures. It is important to recognize that patients who smoke, use alcohol or caffeine on a regular basis, or have ongoing workplace or other chemical exposures may be unable to link their symptoms with specific exposures due to masking.

VI. PROPOSED MECHANISMS

Under the assumption that most of the symptoms described in this chapter stem from a unitary disease process, then the unifying dynamic remains a mystery. Even if one assumes these symptoms arise from multiple causes or different disease processes, their underlying physiological bases are difficult to imagine. Some physicians and researchers view these patients' symptoms as psychogenic phenomena, resembling depression, somatoform disorder, or posttraumatic stress disorder. Others see them as chemically induced and offer various physiological explanations (Ashford and Miller, 1998; summarized in Sorg, 2000). To date, surprisingly little research has been done in this area when one considers the fact that 2–6% of the U.S. population think they suffer from it (see Sec. IV).

Early mechanistic studies focused on immune dysregulation as a potential explanation for these patients' problems. These studies suffered from major methodological limitations, and no consistent immunological abnormality was found (reviewed in Mitchell et al., 2000). To assess inter- and intra-laboratory reliability, Mitchell et al. (2000) sent split blood specimens to six laboratories. Good agreement was found for T-cell subsets, but not for more difficult tests, e.g., immune activation markers. Subsequently, patient and control samples were sent to two validated laboratories for T-cell subset and antibody analyses. Despite these validated laboratories and tests, most of the statistically significant differences between the chemically intolerant subjects and healthy controls were observed in only one of the two laboratories used, the only exception being that CD4+ lymphocyte percentages were higher and CD8+ percentages lower in the chemically intolerant group. Data analysis is ongoing.

A key question is why these people are bothered by low-level exposures that the vast majority tolerate. Doty

et al. (1988) asked whether chemically intolerant individuals might have lower olfactory thresholds. Eighteen patients and 18 controls received graded, low-level concentrations of rose oil (phenyl ethyl alcohol) and methyl ethyl ketone via olfactometer. There were no significant differences in olfactory thresholds; however, during stimulus presentations, the patients had significantly higher nasal resistance and respiration rates. Fiedler et al. (1996a) found no difference in odor identification ability between chemically intolerant patients and controls.

The heightened nasal resistance seen by Doty et al. suggests an inflammatory process, a mechanism proposed by others (Bascom, 1991; Meggs, 1994; Meggs and Cleveland, 1993). Fiberoptic rhinolaryngoscopic examination of 10 chemically intolerant patients whose illness began after a chemical exposure revealed "cobblestoning" of the pharyngeal mucosa, resembling lymphoid hyperplasia, in 6 patients and pale mucosal foci in 8 patients (Meggs and Cleveland, 1993). Nasal biopsies of 13 chlorine dioxide–exposed workers who developed chemical intolerances likewise showed inflammation and nerve fiber proliferation (Meggs et al., 1996). In some specimens, mucosal epithelial cells were detached from the basement membrane and intraepithelial cell junctions were disrupted. Eosinophils did not appear elevated. Further studies incorporating control subjects and blinded assessments are needed.

German investigators have been examining the chemosensory event–related potentials of chemically intolerant patients in response to olfactory (hydrogen sulfide) and trigeminal (carbon dioxide) cues (Hummel et al., 1996), both before and after exposure to a common solvent (2-propanol). While solvent exposure did not affect subjects' odor thresholds, their ability to discriminate odors appeared heightened after solvent versus clean air exposure. No normal subjects have yet been tested. Other investigators propose that odor conditioning may play a role in multiple chemical intolerance (Bolla-Wilson et al., 1989; Guglielmi et al., 1994; Schottenfeld and Cullen, 1986; Schusterman and Dager, 1991; Siegel and Kreutzer, 1997).

Bell et al. (1999) and Sorg (2000) propose that multiple chemical intolerance results from central neural sensitization processes. Neural sensitization is the increased neuronal responsiveness to a stimulus following repeated exposures to the same stimulus or a different stimulus, a form of learning being explored in laboratory animals repeatedly exposed to drugs of abuse, especially cocaine and amphetamines. The limbic and mesolimbic brain regions are particularly susceptible to sensitization, a process that appears to involve excitatory amino acids, which may alter pain perception, olfaction, learning, and memory. In this rodent model, physical stressors, e.g., foot shock and tail pinching, augment stimulant drug responses. Features of this animal model that fit the clinical picture (Sorg, 2000) include the progressive increase in drug/chemical response over time and with additional exposures, the apparent permanence of the sensitivity, the absence of symptoms in the absence of chemical/drug exposure, the greater sensitivity of females versus males, and the spreading of sensitivity to chemically dissimilar substances.

Sorg (1996) hypothesized that sensitization to formaldehyde and other chemicals might affect the same brain pathways involved in cocaine sensitization, e.g., the mesolimbic dopamine system. Rats inhaling 1ppm of formaldehyde 1 hour daily for 20 days, as compared to sham-exposed rats, later showed heightened responses to cocaine. This sensitivity persisted 4–6 weeks post–formaldehyde exposure (when the experiment ended) (Sorg, 1996). Kay (1996) showed that rats exposed to toluene vapors, but not most food odors (except mint), exhibited narrow-band, high-amplitude 15–30 Hz oscillations in the olfactory-limbic tract. Repeated low-level exposure to toluene (below OSHA legal exposure limits) in rats adversely affected their performance of complex learning and spatial memory tasks (Rogers et al., 1999; Von Euler et al., 1993).

Consistent with these limbic changes in animals, chemically intolerant individuals score higher on the McLean limbic system checklist (Teicher et al., 1993), a questionnaire probing symptoms associated with temporal lobe seizures which frequently originate in the limbic system (amygdala) (Bell, 1996). Notably, women with temporal lobe epilepsy have increased rates of self-reported polycystic ovary disease, possibly due to amygdala-regulated release of hypothalamic reproductive hormones. Chemically intolerant women also self-report more menstrual problems than do controls (Bell et al., 1995). In a series of inhalation challenge studies using various low level exposures, Bell et al. (1996, 1997a,b,c) found evidence for sensitization of heart rate, blood pressure, plasma beta-endorphins, and EEG activity in chemically intolerant individuals, but not in controls.

Cholinesterase-inhibiting pesticide exposure has been implicated in the initiation of multiple chemical intolerance and the Gulf War veterans' unexplained illnesses (Cone and Sult, 1992; Haley et al., 1999; Miller and Mitzel, 1995). Rats bred for organophosphate sensitivity show greater susceptibility to various cholinergic agonists but, interestingly, are also less tolerant of nicotine, serotonin agonists, dopamine antagonists, diazepam, ethanol, and sucrose—structurally unrelated substances (Djuric et al, 1995; Overstreet, 1996). These specially bred rats have about 20% more cholinergic receptors in certain limbic regions, including the hippocampus and striatum. When sensitized to egg protein (ovalbumin) via

intraperitoneal injection and subsequently fed ovalbumin, these cholinergically sensitive rats showed greater gut permeability than did control rats (Djuric et al., 1995). Increased gut permeability in humans is thought to underlie various food intolerances. Likewise, inhaled methacholine and inhaled ovalbumin following ovalbumin presensitization via intraperitomal injection resulted in greater airway reactivity in cholinergically sensitive rats than controls (Djuric et al., 1998).

Differences in the ability to absorb, metabolize, and excrete various chemicals might explain why some people are more vulnerable to developing multiple chemical intolerance, for example, decreased sulfation capacity (McFadden, 1996), abnormal porphyrin metabolism (Morton, 1995), or paraoxonase (organophosphate-detoxifying enzyme) deficiency (Costa et al., 1999; Haley et al., 1999). To date, no adequately controlled studies exploring these possibilities have been published.

Other proposed explanations include: (1) neurogenic inflammation—e.g., increased c-fiber neuron density in affected tissues; greater neuropeptide and prostanoid production by susceptible subjects; increased and protracted response to c-fiber activators like capsaicin; increased central autonomic response following c-fiber stimulation; and decreased mucosal neutral endopeptidase; (2) nonneurogenic inflamation—e.g., increased inflammation in affected tissues resulting in augmented neurosensory response; increased inflammatory response to chemical exposure; and (3) altered perceptual and central integration—e.g., differences in adaptation, habituation, cortical representation, perception, cognition, and/or hedonics; different qualitative and quantitative interactions between trigeminal and olfactory systems; different higher integration of sensory inputs (Bascom et al., 1997).

Randolph first noted striking parallels between chemical intolerance and drug addiction (Randolph, 1962), including the presence of stimulatory and withdrawal symptoms, cravings, and cross-addiction/intolerances to structurally diverse substances (summarized in Table 4). In this model, both addiction and chemical intolerance involve a fundamental breakdown in tolerance that occurs only in certain susceptible individuals following repeated exposures, whether to drugs of abuse or to chemicals. It is hypothesized that repeated exposures to drugs or chemicals result in amplified stimulatory and withdrawal symptoms (Miller 1997, 1999). Subsequently, in order to prevent unpleasant withdrawal symptoms, drug abusers take another "hit," and then another, leading to addiction. In contrast, chemically intolerant individuals who link their withdrawal symptoms to alcohol, caffeine, etc., shun these substances, but perhaps for the same reason addicts remain addicted—to avoid withdrawal symptoms. The theory is that toxicant-induced loss of tolerance leads to amplified stimulatory and withdrawal symptoms and that the outwardly polar behaviors of the drug addict and the chemically intolerant patient may both be strategies for avoiding withdrawal symptoms (Miller, 1999, 2001a; Newlin, 1997).

Proposed psychological mechanisms for multiple chemical intolerance include odor conditioning, physician-induced (iatrogenic) beliefs, panic disorder, toxic agoraphobia, posttraumatic stress disorder (e.g., illness resulting from a traumatic chemical spill or childhood sexual abuse), somatoform disorder, and depression (Binkley and Kutcher, 1997; Göthe et al., 1995; Gots, 1995; Guglielmi et al., 1994; Kurt, 1995; Pennebaker, 1994; Simon, 1994; Sparks et al., 1994a, b; Spyker, 1995; Staudenmayer, 1999; Staudenmayer and Selner, 1987; Staudenmayer et al., 1993). Davidoff and Fogarty (1994) examined 10 published studies that explored possible psychogenic theories for chemical intolerance. All drew scientifically unsupportable conclusions concerning cause and effect, and erroneously assumed that psychological symptoms were psychogenic when chemical exposures might also explain them.

Some symptoms these patients report mimic panic disorder, including hyperventilation, lightheadedness, chest discomfort, palpitations, paresthesias, and impaired mentation, leading researchers to wonder whether anxiety underlies chemical intolerance. Eleven of 15 chemically intolerant patients exposed to their own problem triggers, e.g., hairspray or the yellow pages, reported that these reproduced their characteristic responses, including tachycardia, tremor, and pallor (Leznoff, 1997). Exhaled CO_2 in all 11 responders decreased, consistent with hyperventilation due to an anxiety reaction. A few responded to odorless stimuli, e.g., sugar or water, as well. In a single-blind study, Binkley and Kutcher (1997) administered saline (placebo) intravenous sodium lactate (known to elicit attacks in persons with panic disorder) to 5 chemically intolerant patients, all of whom responded with panic-like symptoms. In another single-blind case-control study, 31 chemically intolerant patients and 31 healthy controls inhaled a single breath of air alone or air spiked with CO_2 (35%) (Poonai et al., 2000). Inhaled CO_2 elicits panic symptoms in the majority of patients with panic disorder, but only 5% of healthy controls. Significantly more chemically intolerant patients (71%) than controls (26%) fulfilled panic criteria after CO_2 inhalation. Both groups showed significant changes in heart and breathing rates after CO_2 versus air, with no significant difference between patients and controls. The high percentage of controls responding in this study and the fact that the CO_2

Table 4 Parallel and Opposing Features of Addiction and Abdiction (Chemical Intolerance)

Feature	Addiction	Abdiction
Multisystem symptoms, especially central nervous system symptoms	+	+
Multiple, chemically unrelated substances affecting same individual	+ (cross-tolerance)	+ (cross-tolerance or "spreading")
Caffeine, alcohol, nicotine, drugs implicated	+	+
Size of doses "tolerated" vs. those tolerated by general population	large	small
Inhalation, ingestion, injection or transmucosal routes	+	+
Stimulatory and withdrawal symptoms	+	+
Heightened sensitivity to physical stimuli (noise, light, heat, cold, touch, vibration) during withdrawal phase	+	+
Cravings, bingeing	+	+ (caffeine, foods)
Habituation	+	+
Heightened sensitivity following period of avoidance	+ (e.g., tobacco)	+
Genetic predisposition	+	+
Demographics	Poorly educated males, lower socioeconomic status	College educated females, middle to upper socioeconomic status
Gender ratio (M:F)	2:1	3:5
Age of onset	Teens, 20–30 years	30–50 years
Ill-defined physiological mechanisms	+	+
Lack of biological markers	+	+
Lack of effective drugs for treating condition	+	+
Primary therapeutic strategy	Abstinence	Avoidance
Detox/withdrawal requiring 4–7 days	+	+
Societal views concerning nature of problem	Disease vs. lack of willpower to avoid substances (underavoidance)	Disease vs. belief system leading to avoidance of substances (overavoidance)
Patients viewed as difficult, demanding	+	+
Linked to violence, physical/sexual abuse, suicide	+	+[a]
Disruption of work, family and social relationships	+	+

[a] If chemical intolerance and addiction are interrelated and tend to cluster in families, then the higher rates of childhood abuse described by some investigators (Staudenmayer et al., 1993) among chemically intolerant women conceivably could be the consequence of alcoholic or drug-addicted elders who abused them.

mixture "had a marked taste" suggests study design problems. The other two panic studies cited above did not use controls. Many symptoms of chemical intolerance deviate from the panic profile. Hyperventilation during chemical (or even placebo) exposure in a setting where patients are being scrutinized by researchers and administered chemical challenges does not prove that the illness is psychogenic. A sizable percentage of healthy controls appear to respond similarly. Results of the lactate infusion study do not rule out possible metabolic problems in these patients, e.g., abnormal red blood cell oxygen-carrying capacity. Carefully conducted studies are needed to untangle the current confusion of competing hypotheses. Funding for such studies has been scant.

VII. MEDICAL MANAGEMENT

Forty percent of chemically intolerant patients in one study had consulted 10 or more medical practitioners (Miller and Mitzel, 1995). Some see clinical ecologists, while others remain with their family doctors. Still others seek out aca-

demic occupational and environmental medicine doctors, particularly when workplace exposures are involved. Even physicians familiar with the phenomenon have difficulty managing these cases. Patients are apt to ask about various unorthodox therapies. At this time, controlled studies for any treatments are lacking. Ideally, physicians should not chastise patients who attempt alternative treatments, but display their desire to see the patients improve, help them avoid potentially dangerous interventions, and serve as their advocates during a perplexing illness. "Increasingly, in difficult circumstances, the reasonable trend in medicine is to explain the options and allow the patient to decide" (Vasey, 1995). Ample time should be allotted for visits and/or telephone consultations if patients cannot travel. Often, other patients and support groups can offer assistance.

A multidisciplinary approach, paralleling that used for chronic pain, has been suggested (Weaver, 1996). Weaver advises: "Regardless of the treatment chosen, it is important to emphasize that functional improvement and increased patient control, not cure, are the goals. Complete resolution of odor sensitivity may not be possible." Patients can exhaust their financial resources, their families, and themselves pursuing alternative treatments, when time and money might be better spent modifying their home environment.

Consistently, the single most helpful intervention reported by these patients has been avoidance of problem exposures. In a survey of 206 MCS patients with an average educational level of nearly 4 years of college, 71% rated avoidance of problem chemicals, and 54% avoidance of problem foods, as "very helpful." Although 52% had tried psychological or psychiatric therapies, only 17% of those who had tried them rated them as "very helpful" (Miller, 1995).

DePaul University researchers found that at least three fourths of 305 chemically intolerant subjects who had tried the following interventions found them to be of "enormous" or "major" help: avoiding chemicals that cause reactions (93%), creating an environmentally safe (odor-free) living space (86%), moving to a less polluted area (76%), and avoiding foods that provoke reactions (75%) (LeRoy et al., 1996). In a grass-roots survey of 243 chemically intolerant patients, nearly half of whom were on disability, at least three fourths reported these interventions to be of "enormous help" or "major help": avoidance of chemical exposures (95%), relocation to avoid pollution (79%), and avoidance of problem foods (76%) (Johnson, 1996). Given the patients' clear consensus that chemical and food avoidance benefit them most, increasing numbers of physicians have begun to recommend avoidance strategies for these patients.

While the vast majority of patients view avoidance of odor/chemical and food triggers as paramount (Johnson, 1996; LeRoy et al., 1996; Miller, 1995), psychological support (to be distinguished from traditional psychotherapy) can be helpful in any illness, whether the condition is psychogenic or physical in origin. Some authors have advocated psychological interventions as the preferred or only acceptable treatment modality for multiple chemical intolerance (Sparks et al., 1994b), expressing concern that the illness may be iatrogenic. At this time, placing sole reliance on psychological therapies, to the exclusion of trial avoidance, is at best premature and, at worst, potentially harmful (Miller, 1995). A multifaceted approach is called for, one that includes the identification and avoidance of odor/chemical and food triggers, low- or no-cost alterations of patients' workplace and home environments, and appropriate psychological support.

In the United States, affected individuals must chart their own course to recovery. Balanced medical information and knowledgable, sympathetic physicians are difficult to find. Fatigue and concentration difficulties may undermine care seeking, the ability to identify triggers, implementing lifestyle changes, obtaining social support services, etc.

Chemically intolerant patients frequently report adverse reactions to medications and poor tolerance for standard drug doses. They appear to be at increased risk of developing both known drug side effects (even at low doses) and idiosyncratic reactions (McLellan, 1987). When new symptoms surface, it can be difficult to determine whether they are due to a medication (the drug itself, a dye, excipient, or diluent), an environmental exposure, or some new medical problem, e.g., cancer or coronary artery disease. Exhaustively evaluating each new symptom quickly becomes costly and exposes patients to other risks, including anesthetic agents or x-ray contrast dye, potentially adding more layers of "unexplained" symptoms. Patients may improve as medications are removed from their regimens. Some patients benefit from lower-than-normal drug doses (e.g., analgesics or antidepressants, but not antibiotics), a noteworthy clinical observation consistent with their amplified responses to environmental pollutants. Some find they can tolerate certain drugs better than others and make special requests, e.g., dental anesthetics without epinephrine. Any reasonable request should be honored.

Environmental testing rarely contributes to understanding these patients' health problems. However, professional industrial hygienists or indoor air consultants sensitive to these concerns can help detect contaminant sources and make recommendations for minimizing exposures following a walk-through workplace or home evaluation. These consultants need to be nonsmokers with an excellent sense

of smell. Smokers and passive smokers (as well as workers routinely exposed to petroleum products) are less able to perceive various low-level odors, perhaps as a consequence of sensory deficit or habituation (Ahlstrom et al., 1986, 1987). Indoor air contaminant concentrations of importance for chemically intolerant patients appear to be orders of magnitude below those prescribed by law (OSHA) for occupational environments. Unless exceeded, legally adequate occupational exposure levels have little relevance and should not be invoked.

As for any chronic illness, psychological support may be helpful, depending upon the patient's needs and willingness. Tremendous disruption of work, family, and social lives can occur with this illness, e.g., divorces from spouses who smoke. Suicides have been reported. Support can be provided by psychologists, psychiatrists, social workers, or primary care doctors, although patients rarely find that psychological interventions alter their intolerances (Johnson, 1996; Miller 1995). Actively psychotic or suicidal patients need to be taken seriously and treated and protected accordingly.

Various investigators advocate psychological or psychiatric interventions, but only anecdotal data suggest that these approaches may be helpful (Amundsen et al., 1996; Bolla-Wilson et al., 1989; Guglielmi et al., 1994; Schottenfeld and Cullen, 1985; Spyker, 1995). Several authors claim their patients improved as a result of psychotherapeutic interventions, but adequate follow-up is not provided (Amundsen et al., 1996; Bolla-Wilson et al., 1989; Guglielmi et al., 1994; Schottenfeld and Cullen, 1985; Spyker, 1995). Staudenmeyer et al. (1993) similarly attest, without providing follow-up or appropriate study design, that among their patients who agreed to undergo psychotherapy, 75% had a successful outcome.

Among 243 chemically intolerant individuals who had taken an antidepressant, 10–20% found them of "major" or "enormous" help; 50–65% reported harmful effects; and 10–30% reported they were not helpful or their effect was unclear (Johnson, 1996). Two single-case reports have appeared in the literature involving individuals whose odor intolerances apparently resolved while they were taking selective serotonin-reuptake inhibitor antidepressants, one case involving psychological desensitization as an adjunct (Stenn and Binkley, 1998) and the other using drug alone (Andiné et al., 1997).

Accommodating these individuals in the workplace can be challenging but vital to their self-esteem and livelihoods. Some patients are able to continue working provided that they avoid problem exposures, e.g., coworkers' fragrances or copier machines. Workplace accommodations can include increasing fresh air supply and air circulation, removing business machines (fax machines, copiers, laser printers) from the immediate work environment, providing an alternative work space, removing carpeting, selecting odorless and less toxic cleaning agents, adopting integrated pest management, and allowing employees to work from home (Miller 2001; Miller et al., 1999). Physicians can facilitate the accommodation process by sending reasonable written requests to employers or schools on their patient's behalf, but only with the patient's full knowledge and written consent, so as to protect the physician should the patient's job be eliminated.

Multiple chemical intolerance is increasingly being viewed as a disability (Winterbauer, 1997). Internal memoranda of the Social Security Administration and Department of Housing and Urban Development recognize the illness for purposes of compensation and housing accommodation, respectively. Recent Equal Employment Opportunity Commission (EEOC) statistics show that from November 1, 1993, through March 31, 2000, 564 multiple chemical intolerance discrimination–related complaints were filed against employers, 60% alleging failure to provide reasonable accommodation and nearly 50% wrongful discharge (EEOC, 2000).

The courts have struggled over whether the illness should be viewed as a disability, issuing conflicting opinions. Current law would make it difficult for an employer to claim that a condition that so greatly restricts daily activity is not a disability (Winterbauer, 1997). The Americans with Disabilities Act (ADA) obligates employers to seek inexpensive, practical solutions that will reduce troublesome odorous and odorless (e.g., pesticide) exposures (Winterbauer, 1997). It does not require that a chemical-free workplace be provided.

VIII. ILLNESS COURSE, PROGNOSIS, AND PREVENTION

Few patients report full recoveries, even decades after they become sick. There are those rare individuals whose illness was recognized early in its course, who avoided further exposure, and who appear to have recovered (Hileman, 1991). At this time, early recognition and avoidance of further exposure offer the greatest potential to prevent disability. Difficulties in treating the illness, once entrenched, underscore the importance of prompt action. In one clinical series, chemically intolerant individuals who succeeded in avoiding at least half of their self-reported incitants reported feeling better than did nonavoiders at follow-up 6 months to $2^1/_2$ years after their initial visit (Lax and Henneberger, 1995).

In the future, understanding multiple chemical intolerance will be essential for establishing sound national

and corporate environmental policy. If there is a subset of the population that is especially susceptible to various "odors," i.e., common low-level chemical exposures, strategies to protect these people must be found. If only certain chemical exposures initiate the illness process, then the focus should be on avoiding or minimizing those exposures, for example, preventing chemical spills, prohibiting building occupancy during finish-out, and using integrated pest management. Besides regulating exposures that may initiate the illness, notifying people in advance of anticipated exposures, e.g., reroofing or painting, should be standard practice. Such strategies may protect more vulnerable individuals from becoming sick in the first place and thereby prevent unnecessary and costly overregulation of environmental exposures in the future.

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