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REVIEW

Toxicant-induced Loss of Tolerance

CLAUDIA S. MILLER

Department of Family and Community Medicine, The University of Texas Health Science Center at San Antonio, Texas, USA

Abstract

Drug addiction and multiple chemical intolerance (abdiction) appear to be polar opposites—the former characterized by craving and dependency, the latter by aversion. However, when the two are viewed in juxtaposition similarities emerge, revealing a common underlying dynamic, one which appears to be a new paradigm of disease. TILT, or toxicant-induced loss of tolerance, bridges the gap between addiction and abdiction and has the potential to explain a variety of illnesses, including certain cases of asthma, migraine headaches and depression, as well as chronic fatigue syndrome, fibromyalgia and Gulf War syndrome. This paper argues that both addiction and chemical intolerance involve a fundamental breakdown in innate tolerance, resulting in the amplification of various biological effects, particularly withdrawal symptoms. While addicts seek further exposures so as to avoid unpleasant withdrawal symptoms, chemically intolerant individuals shun their problem exposures, but for the same reason—to avoid unpleasant withdrawal symptoms. These observations raise critical questions: do addictive drugs and environmental pollutants initiate an identical disease process? Once this process begins, can both addictants and pollutants trigger symptoms and cravings? TILT opens a new window between the fields of addiction and environmental medicine, one that has the potential to transform neighboring realms of medicine, psychology, psychiatry and toxicology.

INTRODUCTION

Gulf War veterans and other individuals who report multiple chemical intolerances following exposure to various toxicants (pesticides, fuels, solvents, combustion products, air contaminants in a sick building, etc.) appear to go through much the same addiction cycle—acquisition, maintenance, withdrawal and relapse—as do drug abusers [1] (Table 1). There are certain differences. For instance, repeated drug use leading to addiction occurs more often in males than females, and chemical intolerances are more apt to be reported by susceptible females. However, people in both these groups—drug addicts and chemically intolerant individuals—describe the same stimulatory and withdrawal symptoms in response to a wide variety of substances. Both adopt strategies to avoid unpleasant withdrawal symptoms: the addict does so by taking another hit, while the chemically intolerant person avoids further exposure.

When chemically intolerant individuals first recognize and begin to avoid substances that trigger their symptoms, they experience a withdrawal phenomenon, which mirrors that of drug addicts. Some patients even call this process detox. Associated symptoms include headaches, fatigue, irritability, depression, myalgias and cognitive difficulties, as well as

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TABLE 1. Comparison of addiction and abdiction

Feature	Addiction	Abdiction
Multi-system symptoms, especially central nervous system symptoms	+	+
Multiple, chemically unrelated substances affecting same individual	+ (cross-tolerance)	+ (cross-intolerance or "spreading")
Caffeine, alcohol, nicotine, drugs implicated	+	+
Size of doses tolerated versus 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 socio-economic status	College-educated females, middle to upper socio-economic status
Gender ratio (M:F)	2:1	1:4, 3:5[1]
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 versus lack of willpower to avoid substances (under-avoidance)	Disease versus belief system leading to avoidance of substances (over-avoidance)
Patients viewed as difficult, demanding	+	+
Linked to violence, physical/sexual abuse, suicide	+	+
Disruption of work, family and social relationships	+	+

[1]The 1:4 ratio reflects findings from various clinical studies that may suffer from gender response biases [2]; in contrast, a population-based randomized survey of 4046 subjects conducted by the California Department of Health Services found a 3:5 gender ratio [3].

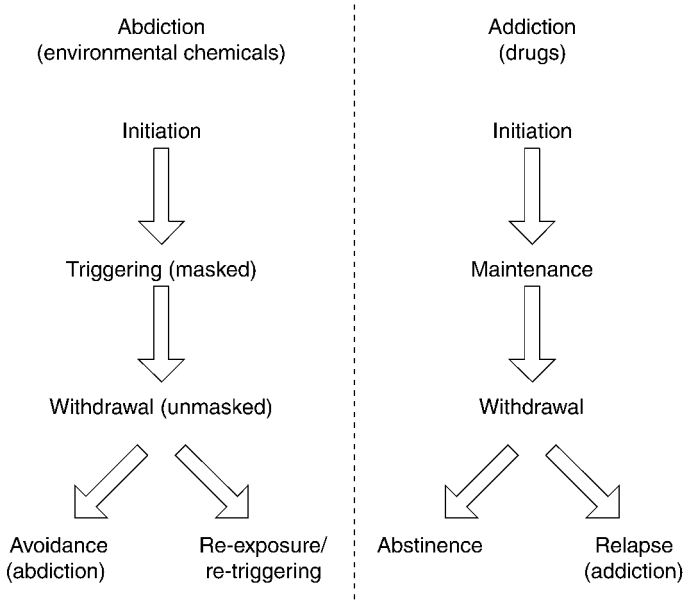

FIG. 1. Mirror relationship between abdiction and addiction cycles.

dyspnea, dysrhythmias and every sort of gastrointestinal problem. During withdrawal, chemically intolerant individuals, like drug abusers, tend to avoid bright light, noise, touch, heat and cold, which are perceived as painful.

Following withdrawal from problem exposures, chemically intolerant individuals arrive at a clean baseline. In this unmasked state, free from background symptom noise, they are able to identify specific triggers and are apt to choose avoidance—'abdiction'—over addiction, shunning caffeine, alcohol, various foods and other environmental triggers. As with drug addiction, re-exposure may trigger cravings, but for these chemically intolerant individuals it is everyday exposures to gasoline vapors, diesel exhaust, fragrances, etc. that set off cravings for chocolate, sweets or other substances, resulting in a fall off the wagon. Chemically intolerant individuals describe hangovers following such lapses. One patient said his responses to chemicals were like being drunk, but without any of the fun parts. Withdrawal symptoms from caffeine, alcohol, etc. may be alleviated, albeit temporarily, by a little hair of the dog.

Add to this equation transitional states, during which patients' symptoms wax and wane, and the addiction/abdiction cycle is complete. The intolerant patient becomes the mirror image of the drug addict (Fig. 1); but what do these parallels tell us about the underlying mechanisms for addiction and chemical intolerance? Recent observations involving chemically exposed groups in more than a dozen countries suggest we may be dealing with an entirely new general mechanism, or theory, of disease, one referred to as toxicant-induced loss of tolerance or TILT (Appendix) [4, 5].[1] TILT appears to involve two steps (Fig. 2):

(1) Initiation—loss of prior, natural (innate) tolerance resulting from a single, high-level chemical exposure, e.g. a chemical spill, or repeated low level exposures, e.g. air contaminants in an office building. This breakdown in tolerance may be caused by one or more toxicant exposures.
(2) Subsequent triggering of symptoms by everyday exposures to common chemicals, foods, drugs, and food/drug combinations (caffeine, alcohol). Symptoms vary from person to person and from one exposure type to another in the same person, but these

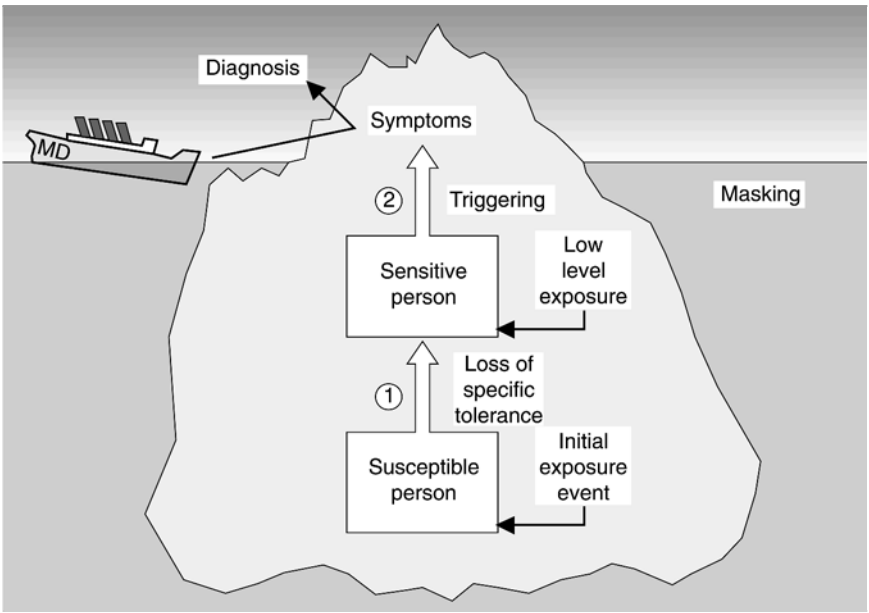

FIG. 2. Phenomenology of TILT. Illness appears to develop in two stages: (1) initiation, i.e. loss of prior, natural tolerance resulting from an acute or chronic exposure (pesticides, solvents, indoor air contaminants, etc.), followed by (2) triggering of symptoms by small quantities of previously tolerated 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 also may go unnoticed (©UTHSCSA, 1996).

individuals report a reproducible constellation of symptoms, or signature response, following each exposure to a particular trigger, for example, headaches with diesel exhaust or dizziness with a fragrance.

Recent surveys in California, North Carolina and New Mexico suggest that approximately 26% of the population suffers from multiple chemical intolerances [1, 6, 7].[2] Many chemically intolerant patients first became sick after a specific, well-characterized chemical exposure. This observation, coupled with the striking parallels between their illness and addiction, raises crucial questions concerning the role of environmental exposures in addiction: do environmental chemical exposures initiate addiction, e.g. via TILT? Are drug addicts especially susceptible to everyday chemical exposures, e.g. gasoline, fragrances, etc.? Do exposures like these trigger symptoms in drug addicts, or set off their cravings?

While it may seem almost inconceivable that in the 21st century we would only now be stumbling upon a new theory of disease, it is worth remembering that other two-step theories of disease that are now widely accepted, i.e. carcinogenesis and the immune theory of disease, were just as controversial in the past century.

Chemical Intolerance: one man's meat is another man's poison

Far more attention and resources have been directed toward understanding the problems of drug addicts than those of people who assiduously avoid drugs of any kind, including caffeine, alcohol, nicotine and medications, for obvious reasons. Drug addicts tend to be

TABLE 2. Triggering exposures reported by 80% or more of people with multiple chemical intolerances who became ill following pesticide or indoor air contaminant exposures [8]

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

disruptive and are often a burden to their families and society, while drug avoiders sit quietly at home and disturb no one. Doctors often have a few patients in their practices who steadfastly refuse to take medications. When no alternative treatment is available and these patients must take drugs, it is often they who develop the side effects and idiosyncratic drug reactions listed in the Physicians' Desk Reference. People who experience adverse reactions to one drug are apt to respond badly to others [9]. In recent years, substance avoiders or abdicts who report intolerances for a vast array of chemicals, foods, and drugs have become an enigma for physicians and researchers in occupational medicine, allergy, and toxicology [10–12]. These individuals say that everyday chemical exposures (Table 2) such as fragrances, vehicle exhaust, new plastic car interiors, household cleaners, etc. cause headaches, fatigue, memory difficulties, mental confusion, anxiety, irritability, depression, myalgias, arrhythmias, dyspnea and every sort of gastrointestinal problem (Table 3).

What has confounded toxicologists and allergists, causing some to discount these patients' claims altogether, are several things. First, the exposure levels or doses said to be causing symptoms are orders of magnitude below established safety limits, leading some scientists to dismiss the illness entirely, on the basis that it violates a fundamental tenet of toxicology—evidence of a dose–response relationship [13]. Secondly, the chemicals these patients implicate are structurally unrelated. This presents a problem for both toxicologists and immunologists who expect chemical receptors, biochemical pathways, target organs

TABLE 3. Symptoms commonly reported by chemically intolerant individuals [8]. Categories were derived via factor analysis of symptoms reported by 112 chemically intolerant individuals who reported becoming ill following exposure to indoor air contaminants ($n = 75$) or cholinesterase-inhibitin g pesticides ($n = 37$)

Neuromuscular	*Cardiac*
Loss of consciousnes s	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	Post nasal 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

and antibodies to be, for the most part, substance or class-specific. Thirdly, the symptoms these patients report seem to be limitless, involving any and every organ system, and often several systems at once, making it impossible to construct a meaningful case definition. Fourthly, the most disabling symptoms are those traditionally addressed by psychiatrists and psychologists—fatigue, mood disturbances and cognitive difficulties. Referral to these specialists is routine.

Despite these reasons why multiple chemical intolerance should not exist, numerous researchers have described identical new-onset intolerances occurring among demographically diverse groups in more than a dozen countries (nine European countries, the United States, Canada, Japan, Australia, New Zealand), groups sharing little in common, save some initial chemical exposure event (Table 4). These groups include radiology workers in New

TABLE 4. Groups reporting new-onset intolerances following well-defined chemical exposure events

Demographic group	Country	Source
Gulf War veterans	United States	[21, 22, 25]
Home owners exposed to pentachlorophenol wood preservatives	Germany	[4]
Home owners, office workers exposed to organophosphate/carbamate pesticides	United States	[8, 27]
Hospital workers	Canada	[4]
Sheep dippers exposed to organophosphate pesticide	United Kingdom	[4, 17, 18]
Radiology workers exposed to film developing chemicals	New Zealand, and other countries	[14]
Solvent-exposed workers	United States	[28, 29]
Office workers, teachers (various indoor air exposures)	United States	[8, 28, 30]
Homeowners, office workers exposed to volatile organic compounds associated with remodeling	United States	[8]
Casino workers exposed to mixed pesticides	United States	[19]
Implant recipients	United States	[25]
Chemical weapons production workers	Germany	[31]
Agricultural workers exposed to organophosphate pesticides	United States	[32]

Zealand exposed to X-ray developer solutions containing glutaraldehyde [14]; EPA employees in Washington, DC, exposed to volatile organic chemicals present in the air of EPA's headquarters building resulting from remodeling, painting and newly glued-down carpeting [15]; families in Germany exposed to pentachlorophenol wood preservative in their log homes [16]; sheep dippers in Great Britain exposed to organophosphate pesticides [4, 17, 18]; hospital workers in Nova Scotia exposed to building air contaminants [4]; card dealers in a Lake Tahoe (California) casino exposed to solvents and pesticides [19]; implant recipients [20]; and Gulf War veterans exposed to solvents, combustion products, pesticides and various drugs during military service [19, 21, 22].

That people from such diverse groups—different occupations, different socio-economic classes, even different cultures—report developing multisystem symptoms and new-onset intolerances following a chemical exposure event is notable, but the fact that they also report new-onset intolerances for alcoholic and caffeinated beverages, medications, and foods—not just chemical inhalants—is a compelling anomaly. In science, compelling anomalies expose the limitations of existing paradigms and drive the search for new ones [23]. Closer inspection reveals that these individuals' intolerances fall into a pattern—one less familiar to allergists and toxicologists than to researchers and providers in the field of addiction [24, 25].

Chemical Intolerance: a troubled childhood

Theron Randolph, an allergist, first described the chemical intolerance phenomenon half a century ago, calling it unwitting addiction, the addiction cycle being transparent to the patient [26]. His voluminous writings on this addiction-like process were viewed with disinterest or dismissed by his fellow allergists. He was a clinician, not an academician. His ideas came at a time when allergy shots were viewed as voodoo medicine or witchcraft within academic medicine circles. In 1906, von Pirquet coined the term allergy, defining it as altered reactivity of whatever origin—a definition broadly embracing amplified responses, whether on an immunological basis or not. But in 1925 European allergists chose to redefine allergy in the narrower context of antibodies and antigens, over the objections of some US allergists. This new immunological definition of allergy prevailed and, with the discovery of IgE in 1967, allergists at last achieved a scientific basis for their practice. These developments proved the death knell for serious scientific study of other untoward reactions, many of which became footnotes relegated to an inauspicious position in the profession. These non-immune-mediated hypersensitivities came to be called intolerances, or idiopathic or idiosyncratic reactions; in Europe they became pseudoallergies; and Randolph [33] and his colleagues, as he said, "were treated as gadflies." Alsoph Corwin [34], Professor Emeritus of Biochemistry at Johns Hopkins, commented upon what he considered the faulty re-definition of allergy adopted by allergists:

> Essentially, the fallacy lies in the confusion of hypersensitivity with immunity and the consequent exclusion from consideration of those cases of hypersensitivity which do not exhibit serological abnormalities. These include many food reactions, drug allergies, and reactions to *environmental pollutants* [emphasis added].

In effect, all of these other intolerances were "defined out" of allergy, despite pleas by some mainstream allergists to keep them in [35, 36].

Perhaps chemical intolerance was simply raised in the wrong family. Had it not sprung from an allergist and been brought up in a professional society that never really understood it, it might have thrived. Patients who consult allergists concerning their chemical intolerances, believing what they have is an allergy, soon find they have knocked on the wrong professional's door. When their skin tests prove to be negative or non-diagnostic they are told that the problem is not an allergy, and are sent away or referred for psychiatric help. These patients have since sought out specialists in occupational and environmental medicine who do understand chemical exposures, take exposure histories and see other patients with neuropsychological symptoms resulting from chemical exposures, e.g. pesticides and solvents.

Chemical Intolerance Finds a Place

Over the past decade, occupational medicine specialists and researchers in related areas have met in a series of federally sponsored scientific symposia, held in response to the growing dissatisfaction and sheer numbers of chemically intolerant people [10, 11, 37]. Participants in these meetings have urged further studies in this area, and despite their divergent views, reached consensus on research agendas, which, if funded, would advance understanding of the problem, but key studies have not yet been funded. The field of occupational and environmental medicine is itself split over this issue. Many practitioners remain doubtful that people can respond adversely to exposure concentration orders of magnitude below those generally recognized as safe, feel ill-equipped to deal with the patients' caffeine, alcohol and food intolerances, and are awaiting scientific proof before committing themselves. At the same time patients are becoming more vocal, with advocacy groups attracting tens of thousands and distributing their own newsletters. Recent US population-based surveys show that multiple chemical intolerance is a major health concern

for up to 6.3% of the population [3], potentially making it the country's most prevalent chemically caused medical condition. Physicians in practice for a quarter century or longer report an exponential rise in the numbers of these patients in their practices [4].

Why this apparent increase? In the United States, there has been a corresponding increase in the production and use of synthetic organic chemicals since World War II—from a billion pounds annually in the early 1940s to 400 billion pounds in the 1980s (US International Trade Commission). The nature of these chemicals has also changed. For example, cholinesterase-inhibiting pesticides, i.e. organophosphates and carbamates, replaced chlorinated pesticides such as DDT on ecological grounds. These new neurotoxic compounds, developed for agricultural use, also worked well for homes, schools and office buildings, controlling pests with few call backs for exterminators. Organophosphates and carbamates now account for nearly half of US pesticide use. Still other synthetic organic chemicals are released from fuels, paints, clothing and consumer products of every description. Ninety per cent of the US population now spends more than 90% of the day indoors, exposed to pesticides, cleaners, fragrances and volatile organic chemicals (VOCs) emitted by new carpet, particle board and furnishings. These airborne chemicals tend to accumulate in modern, sealed indoor environments. Even the air inside vehicles, especially new ones, contains complex mixtures of VOCs emitted by plastic interiors and rubber floor mats. VOCs are also entrained from traffic exhaust and freshly tarred roads. Over the past three generations, exposures such as these have increased exponentially.

Add to this the energy conservation efforts resulting from the oil embargo of the 1970s, when US citizens received tax credits for adding home insulation, caulking cracks, etc. thus further sealing in contaminants. Responding to the energy crunch, the American Society of Heating, Refrigeration and Air Conditioning Engineers (ASHRAE), which sets US consensus standards for fresh outside air in commercial buildings, schools, public spaces, etc. lowered its fresh air recommendations to 5 c.f.m. (cubic feet per minute) per occupant—a six-fold reduction from the 30 c.f.m. standard in 1900.[3] To make matters worse, most homes receive no fresh outside air other than what leaks through cracks, crevices, open doors or windows. With more tightly sealed, energy-efficient structures and less fresh air brought in from outside, VOC concentrations inside homes and work-places crept to unprecedented highs (Fig. 3).

Accompanying this reduction in fresh indoor air, outbreaks of sick building syndrome spread across the United States, most notoriously in the Environmental Protection Agency's (EPA) headquarters in Washington, DC, where several hundred individuals became ill following remodeling and the installation of new carpeting. While most employees recovered when carpeting was removed, several dozen reported a peculiar new problem. When they went to play bridge or poker with friends and were around tobacco smoke or fragrances—exposures that had never bothered them before—they would immediately feel ill, experiencing headaches, fatigue, inability to concentrate and flu-like symptoms. On airplanes, they would feel sick when they smelled other passengers' fragrances or exhaust gases from nearby aircraft. Ten years later, many of these EPA employees are still unable to tolerate such common exposures. Their symptoms are identical to those of chemically intolerant individuals who became ill following exposure to pesticides or solvents [8, 20, 25, 28, 29].

Similar multi-system symptomatology has been observed in veterans returning from the Gulf War [20, 21, 25, 39]. The vast majority of sick Gulf War veterans seen at one Department of Veterans Affairs referral center reported multiple chemical, food and drug intolerances [20]: 78% reported new-onset chemical intolerances since the Gulf War; 40% experienced adverse reactions to medications; 78% described new food intolerances; 66% reported that alcoholic beverages—even a can of beer—made them feel ill; 25% became ill after drinking caffeinated beverages; and 74% of smokers felt sick if they smoked an extra cigarette or borrowed someone else's stronger brand. Eighty-eight per cent reported new intolerances since the war in one of three categories—chemical inhalants, foods and drugs

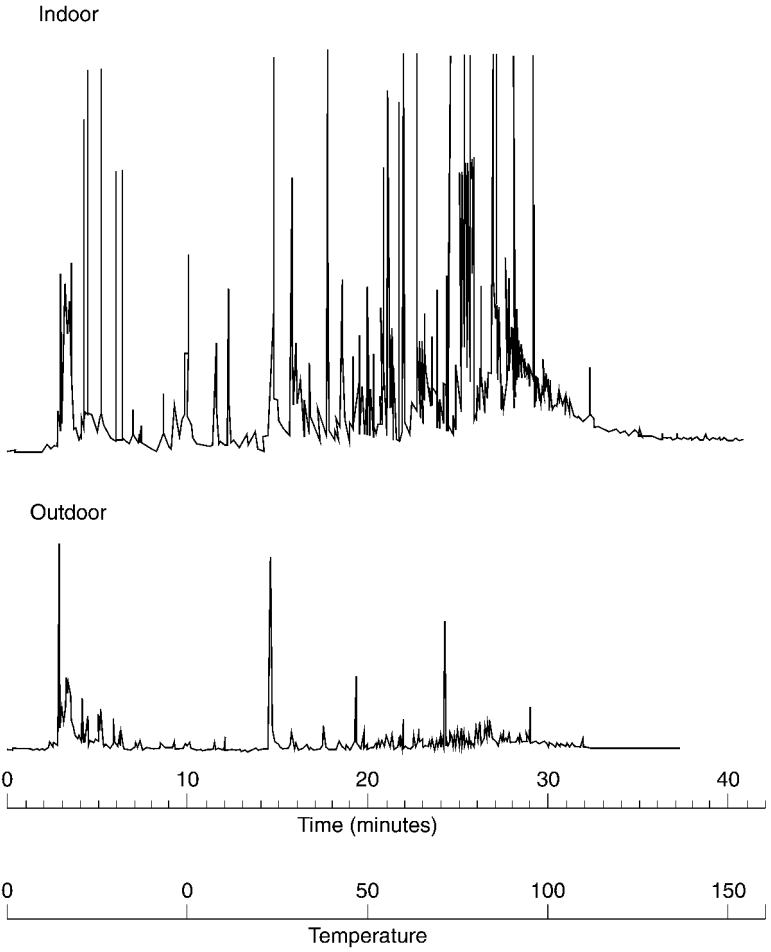

FIG. 3. A comparison of gas chromatographs of equal volume air samples taken inside and outside a complaint office building (Reprinted from [38], with permission from Elsevier Science).

or food/drug combinations—and more than half reported intolerances in all three categories [40].

Inhalant exposures that these sick Gulf War veterans said cause symptoms include engine or traffic exhaust, nail polish or nail polish remover, perfume, pesticides, gasoline, tobacco smoke, fresh tar or asphalt, paint thinner, hair spray, bleach, natural gas, disinfectants and insect repellent. Veteran mechanics reported shakiness, dizziness, nausea, vomiting, headaches and difficulty concentrating when exposed to fuels, solvents or exhaust from aircraft or other vehicles. One mechanic said he can no longer change the oil in his own car and takes it to a quick oil-change shop instead. Another mechanic said that before the Gulf War his idea of the perfect perfume was WD-40. Since the War, one whiff of WD-40 or various other chemicals immediately make him feel ill. Many veterans no longer fill their own gas tanks because the vapors make them spacey or sick. Some refuse to drive because they become so disorientated in heavy traffic or while driving behind diesel trucks that they fear causing an accident; or they have trouble remembering where they parked their cars or where they are going. They get lost on formerly familiar roads. One VA study found a 30%

excess of motor vehicle deaths among Gulf War veterans, which the authors attributed to increased risk-taking behavior [41]. What the veterans say is they become confused, go off the road, mistake the clutch for the brake and have trouble judging stopping distances when they are exposed to gasoline vapors, diesel exhaust or freshly tarred roads.

Fragrances, deodorants and other personal care products commonly trigger symptoms. One veteran sent his wife a favorite fragrance from Saudi Arabia. When he returned from the Gulf she wore it to greet him, but he became so sick during the $2\frac{1}{2}$-hour car ride home he asked her to never wear it again. Several veterans quit wearing their usual colognes or aftershaves. One veteran had purchased 15 different deodorants but was unable to tolerate any of them; another experienced facial paresthesias and shortness of breath from fragrances worn by churchgoers. Many can no longer bear the odor of nail polish or nail polish remover and either left the house or asked their spouses or girlfriends to leave whenever they did their nails.

Other problem exposures for these veterans include enclosed malls; fragrance counters; store aisles with detergents; fertilizers or pesticides; new mobile homes; insecticides sprayed on pets or gardens or during household exterminations; emissions from gas stoves or heaters; exhaust from power mowers, chainsaws, etc.; fabric softeners; fabric finishes on new clothing; insect repellents; and felt-tip markers. Many have given up hobbies or other pastimes involving combustion products or solvents, e.g. refurbishing cars, racing model cars, model building, carpentry, fabric painting, entering dog shows (grooming sprays) and barbecuing.

Studies conducted at the University of Texas, the Robert Wood Johnson Medical School in New Jersey, and the University of Arizona have all noted similar multi-system symptoms and intolerances among Gulf War veterans [20–22, 25]. A CDC study found that ill Gulf War veterans reported more chemical intolerances than did veteran controls.

This intolerance phenomenon is not altogether new. Thirty years ago, Tabershaw and Cooper [32] described 114 agricultural workers with acute organophosphate pesticide poisoning, some of whom had developed persistent symptoms. Several years after their acute exposure, nearly 20% reported that even a whiff of a pesticide made them feel ill. Some quit their jobs for this reason. In 1961, Spiegelberg described persistent, multi-system symptoms among Germans who had manufactured chemical weapons, including organophosphate nerve agent, during World War II [31]. They, too, manifested new-onset intolerances for alcohol, nicotine and medications that continued to bother them more than a decade later.

As compelling as these studies are, they may greatly underestimate the size of the problem: many patients, perhaps the majority, are not even aware they have intolerances, due to a phenomenon called masking (Fig. 4). Masking tends to hide the relationship between an individual's symptoms and triggering exposures. It has several interactive components. One masking component, apposition, occurs when people become intolerant to many different substances [20]. As these individuals go through the day multiple symptoms, triggered by fragrances, hair spray, vehicle exhaust, foods, medications, etc. overlap, creating a confusing array of symptoms. No one cause can be isolated because there is too much background noise (Fig. 4a). Addiction to caffeine, nicotine, or alcohol can also mask the effects of chemical inhalant exposures (Fig. 4b). People exposed to the same substance more than once every 47 days tend to habituate to that substance. Habituation also masks responses (Fig. 4c). Masking helps explain why symptoms vary from person to person, and from day to day in the same individual.

Over the past decade, the finger has been pointed at a number of potential causes for Gulf War syndrome—everything from the oil shroud to pesticides, vaccinations, pyridostigmine bromide, etc. The aforementioned studies of exposure groups in more than a dozen countries suggest that exposure to any one of these Gulf War toxicants or any combination of them could cause a general breakdown in tolerance leading to the plethora of beguiling symptoms associated with TILT. TILT has the potential to explain how Gulf War veterans

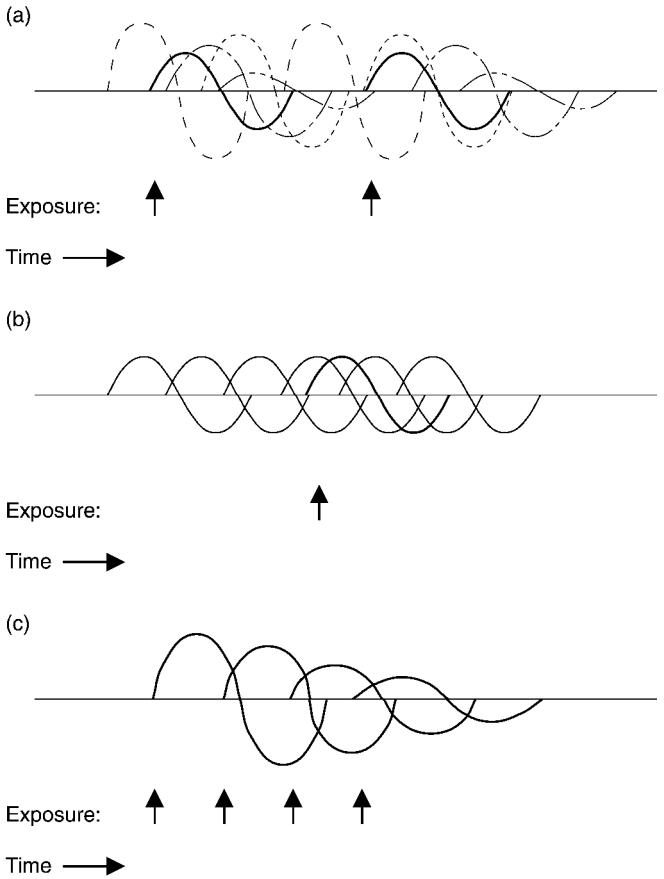

FIG. 4. Components of masking. (a) Apposition. This is the overlapping of stimulatory and withdrawal symptoms. If an individual is sensitive to many different substances, then the effects of everyday exposures to chemicals, foods, or drugs may overlap, producing a confusing array of symptoms. The individual would feel sick most of the time, but the effect of any single exposure would not be apparent to either the individual or his physicians (©UTHSCSA, 1996). (b) Addiction. A person addicted to caffeine, alcohol, nicotine or another substance may take that substance at frequent, carefully spaced intervals in order to avoid unpleasant withdrawal symptoms. These addictants may mask the effects of other exposures, such as chemical inhalants (©UTHSCSA, 1996). (c) Habituation. Symptom severity declines over time with repeated exposures (inhalant or ingestion) to the same substance (©UTHSCSA, 1996).

and other exposed individuals can have symptoms persisting decades after the initiating exposure, even when the initial toxicant is no longer present.

We do not know exactly how this breakdown in tolerance occurs. We do know that rats bred for sensitivity to organophosphate pesticides (the Flinders Sensitive Rat Line) are also intolerant of structurally diverse drugs, including nicotine and ethanol, and have increased gut permeability, which in humans is associated with food intolerance [42]. These rats also over-respond to inhaled methacholine, which causes bronchoconstriction mimicking asthma in humans, and to inhaled ovalbumin, which causes both bronchoconstriction and inflammation, resembling allergic asthma [43]. These observations suggest that the tolerance breakdown may involve the cholinergic nervous system, which regulates vital processes throughout the body. Another possibility is that chemicals might disrupt or

sensitize neural pathways that link the olfactory system with the limbic system in the brain, leading to depression and cognitive difficulties [44]. Several investigators have proposed neural sensitization as a model for multiple chemical intolerance [39, 45]. Memory and addiction appear to be interrelated phenomena [46], which may have some intersection with the memory difficulties caused by chemical exposure in susceptible individuals. The striking parallels between chemical intolerance and addiction suggest they may share the same underlying mechanism, one likely involving multiple neurotransmitters and genetic polymorphisms.

Hierarchy of Addiction: the addiction pyramid

Randolph struggled to find words to describe what he saw in his chemically intolerant patients. Reviewing historical accounts of opiate addiction, he was struck by the similarities between these descriptions and his patients' problems. Seeing congruencies, he envisioned a hierarchy or pyramid of addiction, with the least potent and most slowly absorbed substances (i.e. foods) at the base, and the most potent and rapidly absorbed (heroin, cocaine) at the apex (Fig. 5). Rapidly absorbed substances appeared more addictive. After foods (at the bottom of the pyramid), the next most troublesome addictants tended to be sugars, followed by caffeine-containing drinks, often sweetened with cane, beet or corn sugar. Anecdotally, he noted that reformed alcoholics tend to fall back on caffeine and sugar-containing substances (e.g. chocolate), addicting to them instead. Considerable evidence now links consumption of sweets with excessive alcohol intake in both animals and humans [47].

Tobacco was next in line in terms of addictive potency. Randolph observed tobacco users cross-reacting to other members of the nightshade family, including potato, tomato, eggplant, red and green pepper and chilli. He thought his smokers' adverse responses to these foods differed from their responses to nicotine per se, and believed tobacco companies put sugars into their blends to augment their products' addictiveness.

Near the top of the pyramid he placed inhalant chemical exposures (glues, solvents) and, at the apex, synthetically derived and natural drugs. Drug addicts he saw as living near the tip of the pyramid, while chemically intolerant individuals dwelled closer to the base. However, there is considerable overlap between these two phenomena—addiction and chemical intolerance—occurring in the middle of the pyramid, where the 'food–drug' combinations lie (caffeinated and alcoholic beverages and nicotine in tobacco). In the field of addiction, cross-addiction (called cross-tolerance) to structurally unrelated drugs is widely recognized, e.g. in casinos where the smokers/drinkers/caffeine addicts take their chances at '21' and craps. On the other hand, chemically intolerant people tend to shun these same substances and circumstances. In effect, they 'cross-abdict', but are addiction and abdiction merely opposing faces of the same coin?

The Addiction/Abdiction Interface

This section describes Randolph's early clinical observations and compares them with other investigators' recent findings for chemically exposed groups, especially Gulf War veterans, focusing on the overlap zone between chemical intolerance (abdiction) and societally recognized addiction, that is, responses to foods, caffeine, alcohol, tobacco and drugs—substances lying at the base and middle of the addiction pyramid.

Foods. Randolph's early work on chemical intolerance was founded on a food addiction model developed by Rinkel, who first introduced the concepts of cyclic food allergy and masking [50]. Rinkel described adverse food reactions as being either fixed (constant symptoms) or cyclical (symptoms decreasing with long-term avoidance of a food and

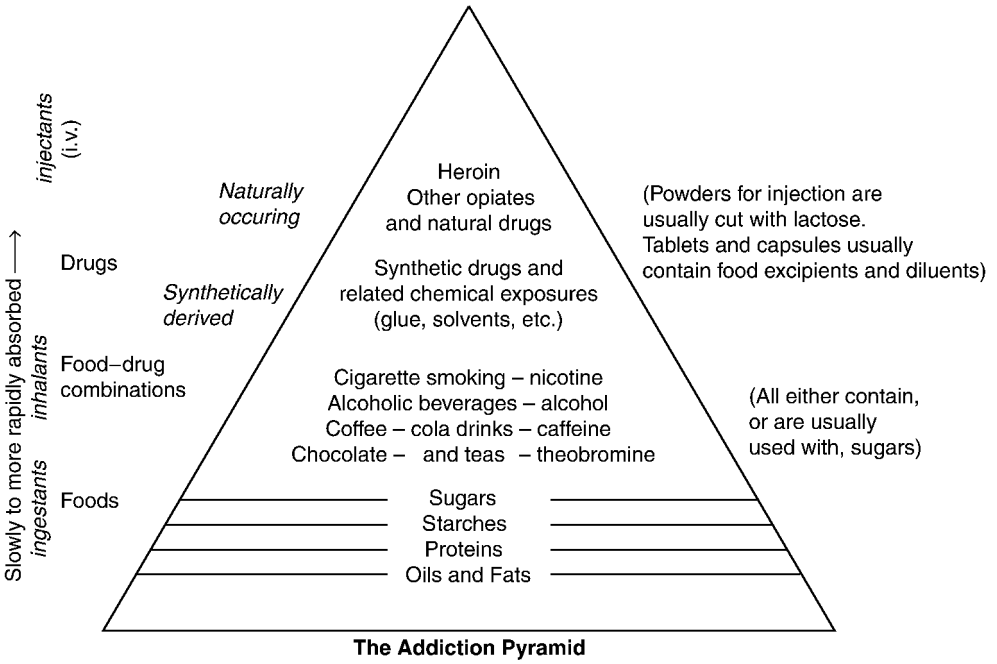

FIG. 5. Addiction pyramid, after [48].

increasing the more frequently the food is eaten). Cyclic food intolerance had both a masked stage and an unmasked stage. Patients became masked if they ate a problem food before their symptoms from the prior ingestion of that same food had subsided. They behaved like drug addicts who take another hit as their withdrawal symptoms set in. Cravings frequently accompanied these withdrawal symptoms, whether foods or alcoholic beverages were involved, observed Randolph.

These cyclic food intolerances, as described by Rinkel and Randolph, cannot be reliably diagnosed using either skin or blood tests. To identify problem foods, patients must first go on an elimination diet during which single foods are eaten, one per meal and spaced 47 days apart, allowing sufficient time for the food to traverse the gastrointestinal tract and for receptors to normalize before a test ingestion. Using this approach, Rinkel determined that his patients' masked food intolerances often involved their favorite, most frequently eaten foods, e.g. corn, wheat, milk and eggs. Frequent consumption of problem foods, even in tiny amounts, maintained their intolerant state.

More recently, occupational medicine specialists have observed this same pattern of cyclic food intolerances appearing in chemically exposed groups. Ninety-seven per cent of 112 chemically intolerant individuals we studied who had become ill after exposure to either pesticides (37 people) or indoor air contaminants (75) reported developing significant food intolerances [8]. Sixty per cent said their diets had been affected a great deal. Consistent with Rinkel's and Randolph's observations, these intolerances involved frequently eaten foods that people often crave, e.g. bread (wheat), corn chips, chocolate, caffeinated beverages, milk, etc.

In 1956, a paper by Randolph entitled 'The descriptive features of food addiction' appeared in the *Quarterly Journal of Studies on Alcohol*, describing how food-sensitive patients are apt to have an immediate, sharp reaction after eating foods to which they are highly sensitive—*if the food is eaten only occasionally* [50]. Such an abrupt let-down

occurring right after the ingestion of an unusual food (i.e. one rarely consumed, such as avocados or cashews) is nearly always recognized and remembered. When the same symptoms occur on several occasions after that food is eaten, people soon learn to avoid it. Such food reactions rarely bring patients in to see their doctors. Just the opposite happens with frequently eaten foods. Patients generally do not recognize foods may be responsible for their fatigue, headaches, mood problems, digestive difficulties, etc. because of masking. In fact, some individuals actually experience a slight pickup or improvement in symptoms shortly after a food is eaten, even craving it because it is so agreeable. Chocoholics are notorious for this.

As opposed to narcotic addicts who know they are hooked, most food addicts have no inkling they are addicted to any foods. Randolph wrote: "Irrespective of terminology—whether this be called masked food sensitivity or food addiction—this is food sensitivity as it most commonly exists." He noted that a food hangover could be alleviated by ingesting more of the food that caused it—the 'hair of the dog that bit you' treatment; and how food addicts who were unaware of their specific food triggers could nevertheless help their hangovers by overeating everything, thereby obtaining relief. Obese patients in his practice were often addicted to corn, wheat, and milk (recent studies suggest that obese individuals often are carbohydrate cravers, and that drugs that increase serotonin neurotransmission tend to normalize food intake and mood [51]. For these patients, dieting, missing meals or omitting salient foods from the diet could precipitate withdrawal symptoms, typically within a day, said Randolph.

Food intolerant individuals tend to be touchy about having their meals on time; delayed or skipped meals make them feel tired, jittery, achy, etc. Eating between meals, before bedtime (to avoid nighttime withdrawal symptoms or awakening), storing food by the bedside or in the car and carrying large cups of coffee or tea to sip all day long help ward off withdrawal symptoms. Food addicts may notice that these maneuvers make them feel better, without knowing why—hence, Randoph's terminology unwitting addiction.

> These patients learn to avoid sharp reactions by eating the foods to which they are allergic at such frequent intervals as for instance at 10:30 A.M., and 3:00, 5:00, and 10:00 P.M. and occasionally during the night, in addition to their three regular meals. Without such interval feedings these patients are inclined to develop midway between their regular meals any one or several of the following symptoms: a gnawing hunger sensation in the abdomen, nasal stuffiness, inability to concentrate, somnolence, extreme fatigue, tenseness, and nervousness [52].

Many sick Gulf War veterans I have seen, as environmental medicine consultant for the Department of Veterans Affairs' regional referral center in Houston, describe new-onset addictions to chocolate, corn chips, and other foods since the war, and report that consuming these foods makes them feel better, at least temporarily. Three-quarters of these veterans report symptoms suggestive of food intolerances, i.e. feeling sick after specific foods (64%) and/or ill after meals (49%). Gastrointestinal symptoms are their most common problem, but these veterans also reported headaches, fatigue, weakness, extreme sleepiness, impaired concentration (mind shuts down) and shortness of breath after meals. Late or missed meals led to weakness (like dying), fatigue, headaches, lightheadedness, dizziness, irritability and abdominal discomfort in nearly 1/5 of the veterans. One-quarter of them described intense cravings for certain foods, consuming prodigious quantities of corn products (popcorn, corn chips), baked goods, pasta, ice cream, chocolate and other sweets. One veteran carried fruit and baked goods in the car because eating them kept him from falling asleep at the wheel.

Caffeine. Some Gulf War veterans I interviewed were consuming as much as 10–30 cups of coffee or tea per day, in an attempt to stave off their fatigue. The majority drank two

to four cups of caffeinated beverages daily and were unaware of any symptoms due to caffeine. Yet nearly all of these individuals suffered from symptoms associated with caffeine sensitivity, including headaches, lightheadedness, irritability, nervousness, diarrhea, abdominal cramps, heartburn, frequent urination, nocturia, heart pounding, nausea and insomnia. One veteran reported headaches after only a few sips of decaffeinated coffee (approximately 10 mg of caffeine per cup). Another, who formerly drank two pots of coffee daily, said he first suspected he was sensitive to caffeine when his spouse left on a trip and he did not bother to make coffee for 4 days. He felt spacey and developed a headache. Thereafter, he reduced his coffee intake to two cups per day. However, if he drinks more than his two-cup allotment, he enters a state of turmoil, becomes lost easily, does not know what to do first or next and becomes obsessive compulsive, double or triple checking things because he cannot remember what he has just done. This same veteran no longer tolerates decongestants, diesel exhaust and certain fragrances, to which he attributes headaches, nausea and dizziness.

Another Gulf War veteran reported severe caffeine withdrawal symptoms after being placed on a psychiatric ward. Although he was consuming the same amount of coffee as before, he did not realize that all of the ward's coffee was decaffeinated. This same veteran also described headaches after drinking one beer; hypersensitivity to the odor of nail polish; nausea around cars burning oil; severe weakness, irritability and headaches if he misses a meal; vomiting after eating onions, garlic or chilli; and lightheadedness and dizziness if he smokes more than his usual 10 cigarettes per day.

Blinded, cross-over studies have shown that some individuals who consume only a single cup of regular coffee per day (about 100 mg of caffeine) reliably develop caffeine withdrawal symptoms when they stop [53]. The question is, have ill Gulf War veterans lost their prior natural tolerance for caffeine? This question can only be answered by removing caffeine and other xanthines from their diets for about a week to see if they get better, and subsequently re-introducing caffeine and seeing whether their symptoms return.

Alcohol. Our studies of Gulf War veterans and chemically intolerant patients suggest that new-onset alcohol intolerance may be the earliest and most robust hallmark of TILT, provided the patient is not a teetotaler [20, 25]. Two-thirds of veterans interviewed at the VA referral center said that their tolerance for alcohol had decreased greatly since the War. One soldier, who before the war drank his friends under the table, now feels inebriated, dizzy, woozy and unable to insert his keys in the ignition after one beer. Some find that as little as one beer causes stomach irritation, jitteriness, nausea, vomiting, slurred speech, flushing, dizziness, abdominal cramps, abdominal swelling, bloating, diarrhea, hot flashes or insomnia. Others experience several days' withdrawal after only one or two drinks.

Nearly half a century ago, Randolph (1956) reported that addictive drinkers appeared to be sensitive to the foods from which their favorite beverages were brewed [50]. He placed 40 reformed alcoholics from his allergy practice on elimination diets which excluded foods contained in their preferred drinks (e.g. corn in bourbon drinkers, grapes in wine drinkers). Several patients developed severe withdrawal symptoms while avoiding these foods in preparation for oral food challenges. When re-challenged with salient foods, these individuals developed intense headaches, fatigue, weakness, nervousness and other symptoms mimicking their former hangovers. Corn, wheat (including barley and rye), grape, cane, potato, beet (sugar), apple and citrus fruits were the most frequent offending foods. To date, no other researchers have unmasked and re-challenged alcoholics in this manner. Consequently, Randolph's findings remain unconfirmed. However, should his observations prove correct, the so-called tolerance that alcoholics exhibit with chronic drinking may in fact be an apparent tolerance, and the acquired tolerance addictionologists describe may actually be masked intolerance. Only careful studies will resolve these important questions and semantic difficulties.

Randolph noted that chemically intolerant patients often become aware first of their alcohol intolerances. He attributed this to alcohol's rapid absorption, and the fact that most people (except alcoholics) tend to use it intermittently. When foods are eaten every day, or even more than once a week, or when they are combined with other foods, patients' responses tend to blur. In contrast with foods, which are absorbed gradually over a period of several hours, alcohol is rapidly absorbed and often consumed on an empty stomach. Thus, symptoms associated with alcohol consumption are more readily perceived. On the other hand, chemically intolerant individuals rarely report alcohol intolerance to physicians, unless asked. Even if they did tell physicians that beer or wine bothered them, most doctors would say that it was best for them not to drink, allowing this key observation to slip by.

Tobacco. Nearly three-quarters of the veterans who had used tobacco reported new intolerances for tobacco products since the Gulf War. Smoking one additional cigarette beyond their usual, or borrowing someone else's stronger cigarette brand, precipitates headaches, lightheadedness, blurred vision, dizziness, spaciness, sore throat, burning eyes, shortness of breath, gagging, coughing, choking sensation, head buzzing, nervousness, irritability, nasal congestion, sinus irritation, chest tightness, nausea or vomiting. Some have switched to lighter brands because their former brands suddenly seemed too strong.

One veteran told me that he had quit smoking cold turkey 2 months before deployment to the Gulf and had experienced no difficulty. During the war, he resumed smoking. After returning home he again tried to quit, but this time became so irritable and edgy that his wife avoided him and he could not kick the habit. This same veteran said he no longer tolerates vehicle exhaust, pesticides, bleaches, phenolic disinfectants, paint thinner and perfume, which trigger lightheadedness, headaches and nausea. He also feels inebriated and stumbles after drinking a small amount of alcohol and experiences intense cravings for chocolate. All these problems developed since the war.

Drugs. Forty per cent of the veterans who had taken medications since the war had experienced adverse reactions. One reported flu-like symptoms lasting several days after each of two methacholine inhalation challenges he underwent. After a steroid injection one veteran became irritable and irrational, yelling at others, ate ravenously and deliberately hit a saw blade with his hand. Another attributed a 20-lb weight gain to fluoxetime, hair loss to terfenadine and arrhythmias to a dental anesthetic. Another experienced chest tightness and chills with radiographic contrast dye, severe headaches from acetaminophen with codeine and elevated liver function tests after taking piroxicam. Individuals who occasionally took decongestant tablets prior to the war with no difficulty whatsoever now find these same drugs leave them feeling strung out, wired, freaked out or hyper. Some have experienced insomnia or chest pain for several days after taking a single decongestant pill. Veterans who had taken antidepressants described panic attacks, nausea, increased heartrate, nervousness, floating feelings and sleepiness with these drugs. Some responded to usual doses of medications as though they were overdoses, e.g. headaches and vomiting with therapeutic levels of theophylline; arrhythmias with antidepressants; vomiting, diarrhea and dehydration after acetaminophen with codeine; and seizures after glyburide. Many veterans reported reacting to various skin contactants, including skin adhesive tape and bandages, topical creams or ointments, jewelry made of plastic or metal including military identification tags, soaps, shampoos, new polyester uniforms, petroleum jelly, wool socks, condoms, cosmetics, deodorant, laundry soaps, fabric softeners and chlorinated spa water.

The responses of chemically intolerant individuals—their symptoms, withdrawals, cravings, etc.—mirror those of drug addicts (Table 5, Fig. 1), with one clear difference: the exposures that bother chemically intolerant individuals are relatively low potency addictants. Some, such as foods, are not considered addictants at all. The question is, are drug addicts and chemically intolerant individuals on opposite ends of an addiction–abdiction

TABLE 5. Symptoms associated with chemical intolerance versus drug withdrawal [55]

Chemical intolerance symptoms	Alcohol	Benzodiazepines	Nicotine	Opiates	Cocaine	Caffeine
Anxiety, agitation	✓	✓	✓	✓		
Appetite increased or weight gain			✓			
Concentration difficulties			✓			
Confusion	✓					
Cravings	✓		✓	✓	✓	
Delirium, hallucinations	✓	✓				
Diarrhea	✓			✓		
Dizziness		✓				
Dysphoria, depressed mood			✓	✓	✓	
Fatigue					✓	✓
Fever	✓			✓		
Headaches						✓
Heart rate decreased			✓		✓	
Heart rate increased	✓			✓		
Hypertension	✓			✓		
Impatience, hostility			✓			
Muscle aches				✓		
Muscle cramps		✓				
Myoclonic jerks		✓				
Nausea, abdominal cramps	✓			✓		✓
Paresthesias, odd sensations		✓				
Perceptual distortion	✓					
Piloerection (“goose flesh”)				✓		
Pupils dilated	✓			✓		
Restlessness			✓	✓		
Seizures	✓	✓				
Sensitivity to light, sound increased		✓				
Sensitivity to pain increased				✓		
Sleep disturbance	✓	✓		✓		
Sleepiness					✓	✓
Sweating	✓			✓		
Tremor, irritability	✓		✓	✓		
Vomiting				✓		
Yawning				✓		✓

continuum? In order to compare drug addicts and chemically intolerant individuals, we need to know what state the patients are in—are they are masked or not? The drug abuser, unmasked, may look just like the chemically intolerant person. For example, Gulf War veterans who formerly drank their friends under the table before the war but now become sick after one beer may have always been sensitive to alcohol, but perhaps their intolerance was masked by frequent imbibing (resulting in habituation) and by responses to other triggers (chemicals, foods, drugs). Did these individuals become unmasked in the Gulf where alcohol was less available? Another possibility is that chemical or drug exposures in the Gulf caused a breakdown in their prior natural tolerance for alcohol and a host of other substances. Or perhaps both of these occurred to varying degrees in different individuals.

People addicted to one drug tend to addict to others, including substances whose chemical structures and pharmacological actions differ, such as alcohol, nicotine and caffeine. This sort of cross-addiction seen among drug addicts mirrors the spreading

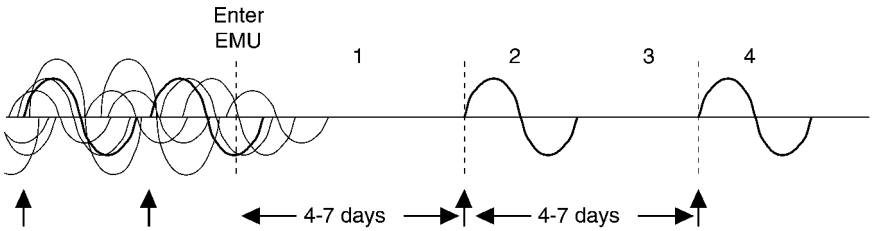

FIG. 6. Use of an environmental medical unit (EMU) in the evaluation of health effects from low level chemical exposures. The figure illustrates stages in the evaluation of a patient in an EMU. At the left, prior to entering the EMU, a patient is experiencing overlapping symptoms in response to everyday 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 trigger challenge, 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.
(4) If the individual is re-challenged with the same substance 4–7 days after the first challenge, the same constellation of symptoms should occur. Challenges involving unrelated chemicals or foods may take place in the interim.

phenomenon (spreading of intolerances to chemically dissimilar agents) reported by chemically intolerant patients. And there are many other parallels between addiction and abdiction (Table 1). The fact that the same veteran who became addicted to caffeine following the war also became abdicted to fragrances, alcoholic beverages, etc. suggests a shared underlying dynamic—TILT.

Challenges

Various economic interests have hindered research on chemical intolerance. Some companies with financial interests at stake hire physicians and researchers as expert witnesses or sponsor their own scientific symposia. Patients see this as the tobacco wars all over again, this time involving not one industry but a host of industries, including carpet and rug manufacturers, fragrance manufacturers, pesticide producers, building owners' associations, etc.

There is little economic incentive to look further into the condition. Researchers find scant funding opportunities in this realm. In the United States, medical research support comes from government sources, e.g. NIH, and pharmaceutical manufacturers, neither of which can be expected to invest heavily in an illness whose very existence remains in question. 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 drug companies to support research to help people who have trouble tolerating medications.

As for Gulf War veterans, at the present time the different specialists they 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. Most veterans have symptoms involving several organ systems simultaneously. For these veterans there continues to be no unifying diagnosis, no known

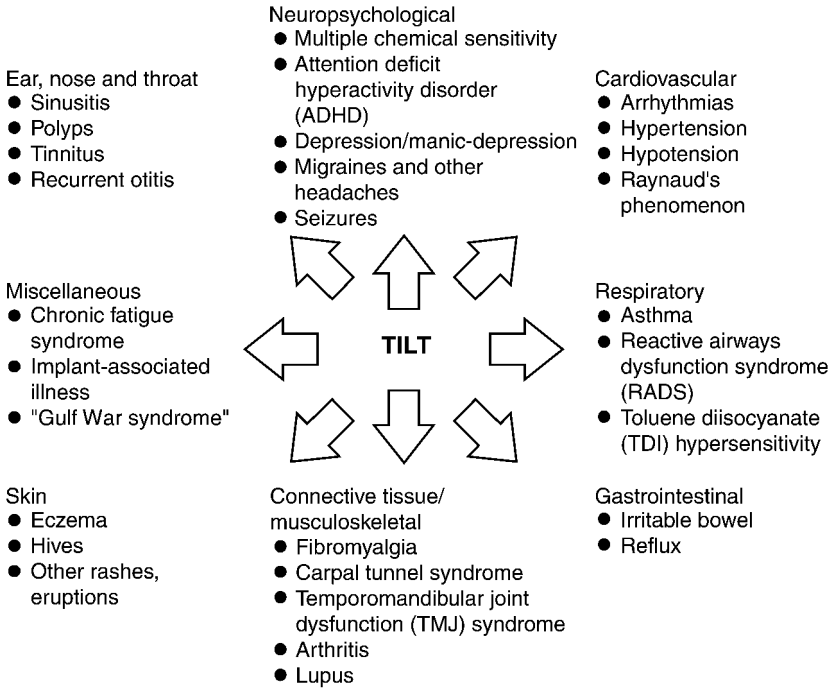

FIG. 7. Conditions that may have their origins in TILT.

etiology and no single identifiable disease process. Notably, 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 [55]. 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 not fever, but the newly acquired intolerances these veterans are experiencing?

TILT may be 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 the oil fires or pyridostigmine bromide pills; those substances have long since left veterans' bodies. It is the aftermath of these exposures, the new-onset intolerances to low-level chemical exposures, which 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.

The confusion clears when the underlying paradigm is understood, and questions that could not be answered are answered:

- For example, why is there no generally accepted case definition? The diverse symptoms these patients report have thwarted any such case definition attempts, which is to be

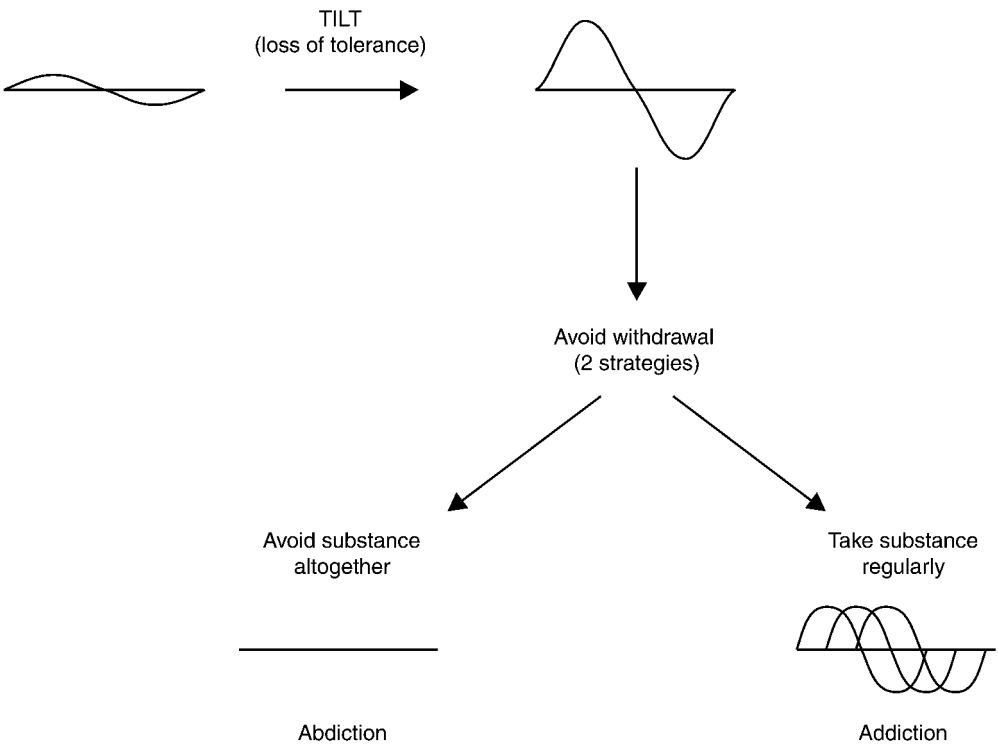

FIG. 8. Relationship between TILT, addiction and abdiction. Prior to TILT, an individual responds normally to an exposure, e.g. caffeine or a solvent, with minimal stimulatory or withdrawal effects. Following TILT, i.e. after a major chemical exposure, responses are amplified. Thereafter, an affected individual avoids unpleasant withdrawal symptoms, either by avoiding the substance altogether (abdiction) or consuming it regularly (addiction).

expected if one is dealing with an entirely new class of diseases, paralleling other disease classes such as infectious diseases or immunological diseases.

- Or, how can structurally unrelated chemicals trigger symptoms, an observation that runs counter to toxicology and allergy, as currently understood? 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:

- Why affected individuals might remain sick years after their initial exposure—as a consequence of subsequent triggering by everyday exposures.
- Why symptoms wax and wane in a bewildering manner—the result of exposures and masking that vary over time.
- Why researchers have been unable to isolate a single culprit exposure underlying Gulf War syndrome—a wide variety of exposures, alone or in combination, appear to initiate TILT, with individual susceptibility and past exposures (including addictants) playing a role.

What is to be derived from all this? That these people are chemically intolerant and those people are addicted, but that sometimes the two conditions seem to coexist in the same individual? Perhaps these two phenomena—addiction and abdiction—are simply different

manifestations of the same underlying disease process, one that is mostly masked in the case of addiction, and unmasked in the case of abdiction (Fig. 8).

Could the same chemical exposures that initiate TILT resulting in chemical intolerance also give rise to food, drug, alcohol and caffeine intolerances and addictions? If so, affected individuals might become addicted to some substances and abdicted to others—all in an effort to avoid withdrawal symptoms. On the surface, addiction and abdiction appear to be opposite behaviors; in truth, what we see may depend on whether the person is masked. Maybe what we are dealing with are not polar phenomena after all, but rather two related symptomatologies which, when brought into apposition, offer a glimpse of the paradigm hidden within.

NOTES

[1] Toxicant-induced loss of tolerance describes a breakdown in prior natural or 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. In this paper, the term tolerance refers to natural tolerance, and habituation is used in lieu of acquired tolerance to describe the diminished effect of an agent on a host following repeated administration. Semantics in this realm are difficult, a frequent 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, object to using sensitization in this manner because there is no evidence that heightened responses to most chemicals are immune-mediated. Instead, allergists invoke the term intolerance for non-immunological adverse responses. In describing TILT, the terms tolerance and loss of tolerance are preferred for several reasons: (1) most physicians and lay persons readily grasp the concept, making new terminology unnecessary; (2) the body's natural ability to tolerate a wide variety of environmental exposures is what appears to be lost; and (3) there is no other readily recognizable term to convey this concept.

[2] There is no widely accepted case definition for multiple chemical intolerance, primarily because patients' symptoms are so diverse. Proposed case definitions for the condition (summarized in [4]) embody similar criteria: chronic, multi-system symptoms triggered by diverse, low-level chemical exposures, with symptoms resolving when exposures are avoided. Bartha *et al.* [56] propose six consensus criteria based upon a survey of 89 clinicians and researchers familiar with, but having divergent views of, the illness [57]: (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* ..." [emphasis added].

[3] In recent years, ASHRAE fresh air requirements for public and commercial spaces have been raised to a minimum of 15 c.f.m. per occupant, 20 c.f.m. in offices, because of health complaints associated with the 5 c.f.m. recommendation [58].

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APPENDIX/GLOSSARY

Toxicant-induced loss of tolerance (TILT)

Proposed general mechanism or theory of disease involving two stages: (1) initiation, i.e. loss of prior natural tolerance resulting from acute or chronic chemical exposure (pesticides, solvents, indoor air contaminants, etc.), followed by (2) triggering of symptoms by everyday chemical inhalants (traffic exhaust, fragrances), foods, drugs, and food/drug combinations (alcohol, caffeine).

Triggering

The provocation of symptoms by a chemical, food, or drug stimulus.

Volatile organic chemicals (VOCs)

Class of chemicals containing one or more carbon atoms that are volatile at room temperature and normal atmospheric pressure. Sources can include cleaning agents, fragrances, tobacco smoke, building materials and furnishings.