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Are we on the threshold of a new theory of disease? Toxicant-induced loss of tolerance and its relationship to addiction and abdiction

CLAUDIA S. MILLER

Environmental and Occupational Medicine, Department of Family Practice, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, Texas

'Toxicant-induced loss of tolerance' (or TILT) describes a two-step disease process in which (1) certain chemical exposures, e.g., indoor air contaminants, chemical spills, or pesticide applications, cause certain susceptible persons to lose their prior natural tolerance for common chemicals, foods, and drugs (initiation); (2) subsequently, previously tolerated exposures trigger symptoms. Responses may manifest as addictive or abdictive (avoidant) behaviors. In some affected individuals, overlapping responses to common chemical, food, and drug exposures, as well as habituation to recurrent exposures, may hide (mask) responses to particular triggers. Accumulating evidence suggests that this disease process might underlie a broad array of medical illnesses including chronic fatigue, fibromyalgia, migraine headaches, depression, asthma, the unexplained illnesses of Gulf War veterans, multiple chemical sensitivity, and attention deficit disorder.

Keywords: *addiction, chemical intolerance, chronic fatigue, environmental illness, Gulf War veterans, multiple chemical sensitivity, theory of disease.*

Introduction

A yet-to-be-proven general mechanism for disease is a *theory of disease* (e.g., the germ theory or the immune theory). This paper addresses the prerequisites a new theory of disease must fulfill prior to its acceptance by the scientific community—anomaly, causality, generalizability, and novelty—and whether toxicant-induced loss of tolerance (TILT) meets these criteria. Also discussed are the implications of this theory for case definitions, biomarkers, medical diagnosis and treatment, and prevention and public health. As a new theory of disease, TILT unites and gives meaning to observations by investigators from more than a dozen countries, offering a new context for scientific discussion, research, and intervention.

TILT is a recently described theory of disease (Miller, 1996a, 1996b, 1997) that is based upon the collective observations of researchers, physicians, and patients in more than a dozen countries over the past half century (Randolph, 1962; Randolph and Moss, 1980; AOEC, 1992; Health Canada, 1992; NRC, 1992; ATSDR, 1994; Ashford and Miller, 1998; Ashford et al., 1995). The TILT theory of disease (Figure 1) posits that following exposure to a single high level, or repeated lower levels, of a chemical or mixture of chemicals, certain individuals lose specific tolerance for various chemicals, foods, and drugs (initiation phase) (Miller, 1997). Subsequently, everyday exposures to these substances trigger symptoms, thus perpetuating illness (triggering phase). 'Loss of tolerance', as defined by a recent federally sponsored consensus panel (Miller et al., 1997), is ''the loss of prior natural or native tolerance'', parallel to a diabetic's loss of tolerance for sugar. [1]

1. Abbreviations: EMU, Environmental Medical Unit; TILT, toxicant-induced loss of tolerance.

2. Address all correspondence to: Claudia S. Miller, M.D., M.S., Associate Professor, Environmental and Occupational Medicine, Department of Family Practice, Suite 610-L, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78284-7794. Tel.: (210)567-7760. Fax: (210)567-7764. E-mail: millercs@uthscsa.edu

[1]When addictionologists use the term 'tolerance', they mean 'acquired tolerance', as might occur in an addict following repeated use of a drug. Here and in our other papers, when we use 'tolerance', we mean 'natural tolerance'. To avoid confusion, we use the term 'habituation', instead of 'acquired tolerance', when describing the diminished effect of an agent on a host following repeated administration of a substance. Semantics in this realm are difficult. TILT is caught between allergy and addiction in this regard. Addictionologists prefer the term 'sensitization' to describe heightened responses in an individual following repeated exposure to a drug. Allergists, on the other hand, have objected to use of the term 'sensitization' to describe heightened responses to most chemicals because there is no evidence that those responses are immune-mediated. Instead, allergists use the term 'intolerance' to describe adverse responses that do not appear to involve antibodies. We have chosen to use the terms 'tolerance' and 'loss of tolerance' because (1) most physicians and laypersons readily grasp the concept; (2) the body's natural ability to tolerate a wide variety of exposures in the environment is what appears to be lost; and (3) we are at a loss to find any other generally recognizable term to convey this concept, and wish to avoid inventing a new term.

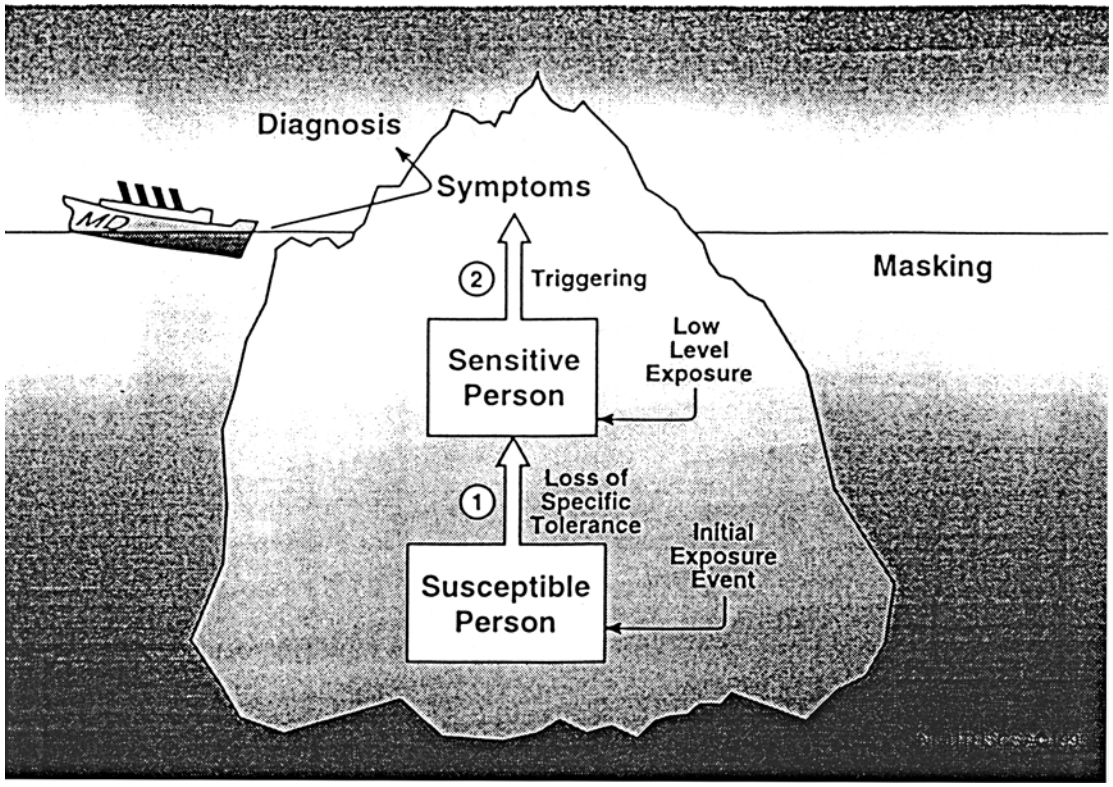

Figure 1. Phenomenology of TILT. Illness appears to develop in two stages (depicted in the portion of the iceberg below the waterline, not visible to the physician): (1) loss of specific tolerance following acute or chronic exposure to various environmental agents such as pesticides, solvents, or air contaminants in a sick building; followed by (2) triggering of symptoms by very small quantities of previously tolerated chemicals, foods, drugs, and food/drug combinations (alcohol, caffeine). A physician (represented by the ship) sees only the tip of the iceberg—the patient's symptoms—and formulates a diagnosis based upon them. Because of masking (due to habituation and overlapping of multiple responses), both physician and patient may fail to recognize that everyday, low-level exposures are triggering symptoms. Even if such triggers are recognized, an initial exposure event that could have initiated loss of specific tolerance might not be noticed or linked to the patient's illness (©UTHSCSA 1996).

'Triggering' was defined as the provocation of symptoms by a chemical, food, or drug stimulus (Miller et al., 1997).

There is accumulating evidence for this two-step process. Reliable observers have described new-onset intolerances following identifiable exposures in demographically diverse groups. These groups include radiology workers from several countries exposed to X-ray developer solutions (Genton, 1998), EPA employees in Washington, DC, exposed to volatile organic chemicals outgassing from new carpet and other office materials (Hirzy and Morrison, 1989), home owners in Germany exposed to pentachlorophenol wood preservative used in log houses (Ashford et al., 1995), sheep dippers in Great Britain exposed to organophosphate pesticides (Stephens et al., 1995; Monk, 1996; Ashford and Miller, 1998), 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), and Gulf War veterans exposed to a wide variety of substances during military service (Fiedler et al., 1996; Miller, 1996b; Ashford and Miller, 1998; Miller and Prihoda, 1999). Despite the demographic diversity of these groups and the heterogeneity of their exposures, all exhibit multi-system symptoms and new-onset intolerances for common chemical exposures, foods, drugs, alcoholic beverages, and caffeine. Symptoms vary from person to person within each exposure group. These observations conform neither to currently understood mechanisms of toxicity nor to any other generally accepted explanation for disease (Waddell, 1993): symptoms appear to occur in response to structurally diverse substances at exposure concentrations that are orders of magnitude below established thresholds for toxicity.

A theory of disease is a yet-to-be proven *general mechanism* for a *class of diseases*, e.g., the germ and immune theories of disease. In the evolution of a new theory of disease, there is invariably an early observational phase during which anecdotal cases are noted and described. As clinical observations accumulate, a corrigible, tentative hypothesis is formulated, e.g., some 'germ' must be transmitted from one organism to another, or the host must form an 'antibody' of some sort directed against an

'antigen'. Armed with this crude theory, scientists next search for biological markers and other evidence that might elucidate the process.

Background

Although the first case report of multiple chemical intolerances (then called 'the petrochemical problem') appeared in the medical literature almost half a century ago (Randolph, 1962), scientific knowledge in this area remains scant. Recent studies suggest that 4–6% of the U.S. population report significant health problems that they attribute to chemical intolerances (Bell et al., 1996; Kreutzer and Neutra, 1996; Meggs et al., 1996). Yet only in the past decade has this enigmatic illness become the subject of several federally sponsored meetings held in Canada and the United States.

Why has recognition of this problem come so late? There may be several reasons. First, TILT appears to involve *two* steps—initiation and triggering. Our awareness of other disease mechanisms involving two steps, namely allergy and carcinogenesis, did not develop until this century. Not unexpectedly, unraveling a process involving two steps is more challenging than one involving a single step. A second reason for TILT's belated recognition may be the fact that not everyone who is exposed becomes sick. In fact, often only a small percentage of those at risk is affected, just as only a minority of persons who are stung by bees become hypersensitive to their venom and are subject to anaphylaxis. A third reason TILT may have escaped our attention until now is that it generally occurs following exposures to petrochemicals whose production has risen exponentially since World War II. Physicians who have been cognizant of this problem for several decades report that the number of patients reporting chemical intolerances has increased over the same time frame. The fourth and perhaps most important reason for this mechanism's delayed recognition is masking.

Masking has been defined by a consensus panel as the ''hiding of responses to triggers due to overlapping of responses to multiple exposures and due to habituation'' (Miller et al., 1997). Patients with this problem often use the terms 'masked' and 'unmasked' to describe their physiological 'state' at a given point in time, i.e., whether they are being exposed to substances that are triggering symptoms (masked), or are avoiding triggers (unmasked). The masked state occurs when responses to triggers overlap in time, thus creating background noise that hides the signal resulting from a particular exposure. The 'unmasked' state occurs when patients avoid triggering substances. Unmasked patients are, in effect, at a clean baseline. If exposed to a trigger (chemical, food, or drug incitant) while in this state, they say they are able to discern specific symptoms occurring in response to that trigger.

Masking is a hypothetical construct, albeit one based upon observations by numerous patients and clinicians. Consensus recommendations for its testing emerged during a recent federally sponsored conference on chemical sensitivity (Miller et al., 1997).

This paper examines the question, could we be witnessing the emergence of a new theory of disease? If so, would we recognize it? What would it look like? What characteristics would it need to have in order to qualify as a theory of disease? Does TILT have these features? Finally, what might be the potential ramifications of this theory, if confirmed? How might it affect our research strategy, approaches to diagnosis and treatment, and environmental and public health policies related to pesticides, indoor air pollutants, new carpeting and other consumer products, use of fragrances, industrial exposures, and hazardous waste sites?

At stake here is our understanding of the role of everyday environmental exposures in a host of chronic, costly medical conditions ranging from chronic fatigue syndrome, multiple chemical sensitivity, fibromyalgia, arthritis, and implant-related illnesses to depression, anxiety, headaches, irritable bowel syndrome, asthma, and the unexplained illnesses of Gulf War veterans. Soaring medical and legal costs and contentious treatment and policy questions compel us to determine whether chemical exposures can cause these conditions. No longer will it suffice to invoke default psychological diagnoses such as depression, somatoform disorder or 'stress' to explain these and other conditions when we have barely begun to explore the eminently testable role of chemical exposures. We cannot afford to assume that just because psychological symptoms occur in some patients, the problem is psychogenic (Davidoff and Fogarty, 1994). A fractious 'chicken or egg' debate as to the origins of chemical sensitivity currently divides the medical community, e.g., 'Is depression the *cause* or the *result* of chemical intolerances?' This debate is reminiscent of the Nineteenth Century struggle over the origins of microbes, i.e., 'Do they arise via spontaneous generation or are they transferred from another source?' In time, careful science settled the question.

Prerequisites for a new theory of disease

There are several prerequisites for the emergence of a new theory of disease. These include: (1) the description by reliable observers of a condition that does not fit existing paradigms for disease (anomaly); (2) evidence of a causal relationship between an exposure or agent and the condition (causality); (3) general applicability of the causal relationship to a *class* of agents and a *class* of diseases (generalizability); and, ultimately, (4) confirmation that the

hypothesized mechanism is in fact new and not simply a variation on a mechanism of disease previously described (novelty).

Anomaly

Before a new theory of disease is proposed, some clinical feature or response that is anomalous must be observed. In the last century, the anomalous observation that some individuals who recovered from a disease did not contract it a second time paved the way for the immune theory of disease. Anomaly is the *sine qua non* for a new theory's emergence. Kuhn (1970) observed that new theories are "generally preceded by a period of pronounced professional insecurity...generated by the persistent failure of the puzzles of normal science to come out as they should. Failure of existing rules is the prelude to a search for new ones."

The anomaly that led to this American Chemical Society meeting on chemical sensitivity, as well as four major federally sponsored meetings on the same topic over the past decade, is the collective and increasingly frequent observation by clinicians of individuals who report multiple chemical intolerances following an identifiable chemical exposure event. The fact that these individuals represent diverse demographic groups (e.g., office workers, sheep dippers, casino workers) who share little in common, save an identifiable precipitating exposure and the subsequent development of new intolerances, is a noteworthy anomaly.

Causality

The second prerequisite for a new theory of disease is that the exposure or agent under scrutiny, whether a germ, antigen, or chemical, must *cause* the observed illnesses. Causality here is defined as "the relation between a cause and its effect or between regularly correlated events or phenomena". Early in the study of a phenomenon, there may be only the *suggestion* of a casual relationship. Later, as the science ripens, postulates or criteria that must be fulfilled in order to confirm causation are established, e.g., Koch's postulates for the germ theory of disease. Various sets of criteria for establishing causality in a rigorous and scientific manner have evolved for viral diseases, immunological diseases, slow infections of the central nervous system and chronic diseases. Nine criteria of Hill (1965)—strength of the association, consistency, specificity of the association, temporality, biological gradient, plausibility, coherence, experiment, and analogy—assist in establishing causality for environmentally induced illnesses (for a discussion of Hill's criteria and their applicability to chemical sensitivity, see Miller, 1996a). Concerning his criteria, Hill cautions that no *single criterion* by itself is sufficient to prove, and absence of any one does not revoke, a possible cause-and-effect relationship. It is in the *aggregate* that his criteria *assist* in confirming causation. Note that Hill speaks of 'confirming', rather than 'proving', causation. Indeed, even the best theories are never proven. They simply are confirmed again and again.

For TILT, as for allergy and carcinogenesis, two sequential steps appear to be involved (in the case of TILT—initiation and triggering). The approaches needed to establish a causal relationship in each of these steps may be quite different. Validation of causation for the first step, initiation, likely will require confirmatory evidence from animal studies and epidemiological investigations. On the other hand, validation of the second step might best be achieved via direct experiment (i.e., human challenge studies)—the single criterion that Hill said provided the strongest support for causality. Thus, the triggering phase of TILT offers a causal hypothesis that can be tested directly in humans. This is in contrast to most other environmentally related conditions, such as lead poisoning or cancer from asbestos exposure, for which provocative challenge in humans would be regarded as unethical.

A recent scientific consensus panel addressed the question—Which stage of TILT, initiation or triggering, should scientists explore first (Miller et al., 1997)? The second stage, triggering, was elected for two reasons. First, as discussed above, the triggering phase lends itself to direct challenge testing in humans. Second, if double-blind, placebo-controlled human exposure studies using common triggers were to demonstrate that most patients' symptoms were psychogenic, there would be no need to undertake the many epidemiological and animal studies necessary to understand initiation. Currently, there is no generally accepted animal model for TILT, and the relevance of recently proposed animal models (Overstreet et al., 1996; Sorg, 1996; Rogers et al., 1999) to the human condition no doubt will be the subject of protracted debate. Likewise, epidemiological studies can only suggest an association, not prove causation. While the funds needed for studying triggering are substantial, they are much less than those required for multiple, large-scale epidemiological and animal investigations (recalling the number and cost of studies that were needed to confirm that tobacco smoke causes lung cancer). Thus, the panel recommended that the second stage of TILT—triggering—be studied first. A set of postulates that would need to be met in order to confirm that an individual's symptoms were triggered by a particular exposure has been published (Figure 2) (Miller, 1997; Ashford and Miller, 1998).

Generalizability

The third prerequisite for a new theory of disease is that it must be generalizable, i.e., the theory must apply to a *class of causal agents* (e.g., to many different germs, or to many different antigens) and must provide a plausible explanation for a *class of diseases* (i.e., an array of conditions involving various organ systems, and not just a single illness).

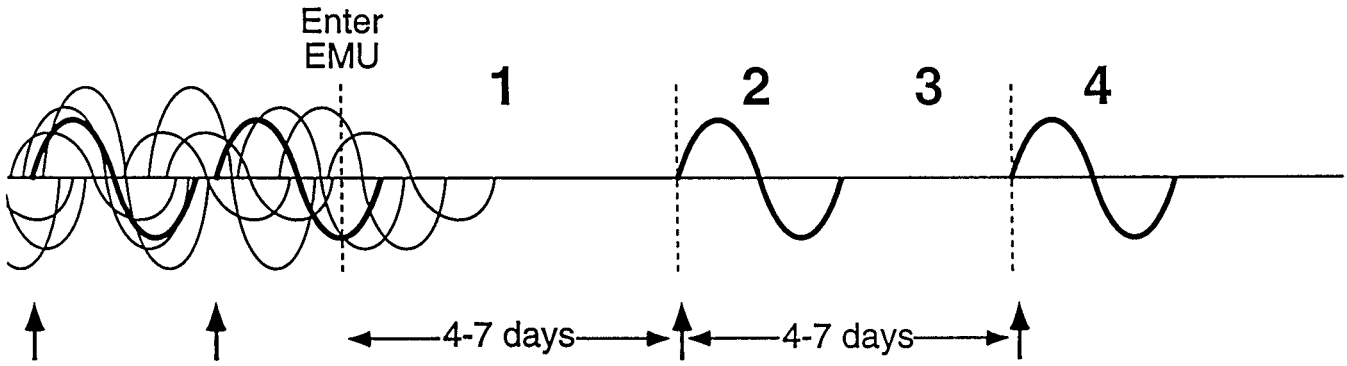

Figure 2. Testing TILT postulates (triggering) using an environmental medical unit (EMU). In the leftmost portion of the figure, before entering the EMU, a chemically intolerant individual is experiencing symptoms in response to multiple exposures (chemicals, food, drugs). Effects overlap in time and the patient's symptoms may appear to wax and wane unpredictably over time. Because of this 'background noise', the impact of any particular exposure cannot be distinguished from those of other exposures. **Postulate 1:** When all chemical, food, and drug incitants are avoided concurrently, remission of symptoms occurs. Anecdotally, many patients report going through 'withdrawal' or 'detox' for the first several days and experiencing increased symptoms such as irritability, headaches, and depression. After 47 days of avoidance, the patient should be at a clean baseline and, if chemically intolerant, free of associated symptoms. **Postulate 2:** A specific constellation of symptoms occurs with re-introduction of a trigger. **Postulate 3:** Symptoms resolve when the trigger is again avoided. **Postulate 4:** Re-exposure to the trigger within an appropriate window of time (approximately 47 days after the last exposure) produces the same symptoms. For research purposes, challenges should be conducted in a double-blind, placebo-controlled manner (©UTHSCSA 1996).

Generalizability here means "applicability to every member of a class, kind or group". In 1868, Max Boehr described the generalizability of the germ theory of disease, noting that "the theory of infection has the characteristic of all good pathological theories; it provides a unified, clear, and entirely intelligible meaning for a whole series of anatomical and clinical facts and for the relevant experiences and discoveries of reliable observers..." (Carter, 1985). In earlier papers, we have described TILT's potential to unite currently disparate clinical observations and conditions, including cases of asthma, depression, chronic fatigue, fibromyalgia, and headaches (Figure 3). Testing individuals with these conditions in an environmentally controlled hospital unit, i.e., a hospital ward in which background chemical exposures have been reduced to the lowest levels practicable in order to determine whether

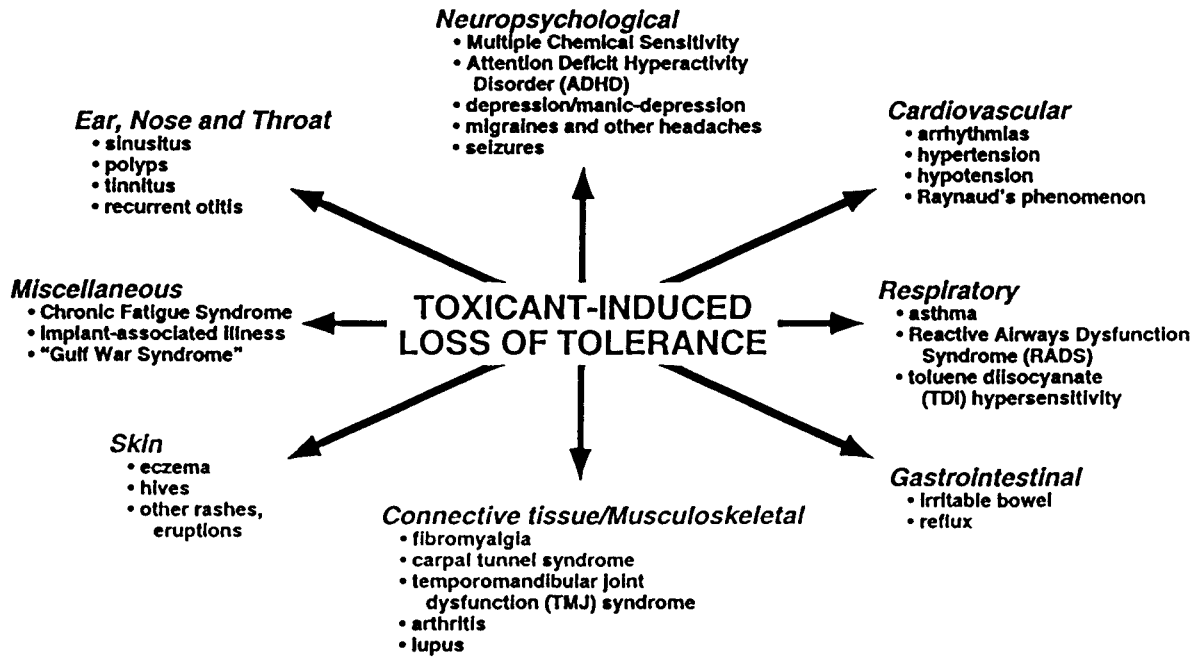

Figure 3. Some conditions that may have their origins in TILT (©UTHSCSA 1996).

patients improve when triggers are avoided and whether their symptoms recur when double-blind, placebo-controlled challenges are administered, will enable us to evaluate whether these and other conditions result from environmental exposures.

The societal value of a theory of disease lies in its enabling us to generalize with such accuracy that we can in fact predict illness. The TILT theory offers a mental model, one which allows us to forecast that a *subset* of persons exposed to chemical spills, to air contaminants in sick buildings, or to pesticide applications will develop symptoms that persist long beyond the initial exposure event. We can predict that those affected will exhibit heterogeneous, multi-system symptoms, especially neurological and psychological (vs. psychogenic) symptoms. They will report new intolerances for common chemical exposures, including fragrances, traffic exhaust, and cleaning agents; new food intolerances (or, if masked, feeling sick after meals); and adverse reactions to medications prescribed for their ills. The more masked they are, the fewer intolerances and triggers they may recognize. As they reduce their exposure to various triggers (unmask), the more robust and discernible their responses to specific triggers will become. These predictions also enable us to intervene, to either halt the exposure or to withdraw from further exposure those who may be more susceptible, so as to prevent chronic illness.

Charles Darwin, whose own theories evolved from his tenacious application of taxonomy, observed that ''Science consists of grouping facts so general laws can be derived from them''. TILT likewise offers a unified theory, as it is the distillate of physician's observations of thousands of cases. As such, TILT fulfills the criterion of generalizability. This generalizability enables us to predict future occurrences of illness, whether after a chemical spill, a sick building episode, a pesticide application, or a war involving diverse chemical exposures.

Novelty

In addition to anomaly, causality, and generalizability, a new theory of disease must provide a truly novel explanation for the illness under study. 'Novel' means that someone has not described the theory before. If the explanation turns out to be a variation on a mechanism that is already known, then it is not novel.

Earlier papers describe more fully the features of TILT that set it apart from current concepts of allergy and toxicity (Miller, 1996a, 1997). Although TILT shares key features of allergy and toxicity, it does not adhere to all of the rules for either of these. For example, although both toxicity and TILT involve adverse responses to environmental chemicals, the doses associated with TILT are orders of magnitude below established thresholds for toxicity for most agents. In other respects, TILT resembles allergy. Both entail a two-step process and subsequent 'hypersensitivity'. Indeed, chemically intolerant patients have in the past referred to themselves as 'allergic' to various chemicals, foods, or drugs (and were upbraided by allergists for using the term in this manner). However, neither IgE nor any other antibody has been shown to play a role in chemical intolerances. Further, allergies involve the interaction of *specific* antibodies with *specific* antigens, in contrast to the spreading of sensitivities to structurally diverse chemicals, foods, and drugs that is the hallmark of TILT.

What, if anything, distinguishes TILT from existing immunological or neurological mechanisms of disease? Notably, the responses of some chemically intolerant persons to certain triggers bear a striking resemblance to the responses of some addicts to drugs (Table 1). Both appear to involve stimulatory and withdrawal phases, as well as individual differences in vulnerability (Randolph and Moss, 1980). The substances that chemically intolerant persons avoid, however, extend well beyond classical drugs of addiction to combustion products, fragrances, pesticides, and common foods.

Is it conceivable that chemical intolerance might involve some of the same biochemical pathways that are involved in addiction, pathways about which we know relatively little, and for which we lack objective clinical tests or markers? In earlier work (Miller, 1996a, 1997), we proposed that chemical intolerance might represent the 'flip-side' of addiction: addicts move toward their favored substances (L. *ad* 'toward' + *dicare* 'proclaim'). Patients who are chemically intolerant move away from some of the same substances (alcohol, nicotine, caffeine, medications, and other drugs). Is this then 'abdiction' (L. *ab* 'away from'), the counterpart of addiction? Newlin (1997) proposed some possible ways in which addiction (to drugs) and abdiction (from chemicals) might be related. First, they might be polar opposites with some clinical features that are diametrically opposed. Second, they might have the same diathesis that is expressed alternatively as abdiction or addiction. Or, they could be unrelated.

Notably, many chemically intolerant patients report that they experience withdrawal symptoms such as headaches, irritability, and malaise during the first few days when they avoid triggers such as caffeine, alcohol, nicotine, and certain foods. Some also describe intense cravings for these substances. Is it possible that chemically intolerant patients, in contrast to substance abusers, experience less of the pleasurable stimulatory effects and/or more of the unpleasant withdrawal effects of drugs and, consequently, avoid many of the same substances? One chemically intolerant patient described his responses to chemicals as ''sort of like being drunk, but without any of the fun parts''.

In the case of addiction, it is well-known that cross-tolerance (acquired tolerance is meant in this case) occurs, i.e., persons addicted to one substance tend to become

Table 1. Parallel and opposing features 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 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, binging	+	+ (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
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 (under-avoidance)	disease vs. 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	+	+

addicted to others, including substances that are *structurally dissimilar*, e.g., alcohol, nicotine, and caffeine. One need only visit Las Vegas to witness such cross-addiction firsthand. Perhaps the spreading phenomenon (spreading of intolerances to chemically dissimilar agents) reported by multiple chemical sensitivity patients is, in fact, cross-*intolerance*, the counterpart to cross-tolerance. The TILT theory posits that repeated, involuntary chemical exposures, such as daily exposure to air contaminants in a sick building over a period of weeks or months, can cause intolerances to develop. These unwitting exposures may be the parallel of substance abuse. Obviously, the sick building occupant is not deliberately imbibing. The body, however, would not distinguish between voluntary and involuntary exposures.

This suggests an interesting possibility: Could both abdiction and addiction be *initiated* by chemical exposure? Indeed, why not? Among the Gulf War veterans the Department of Veterans Affairs has asked me to evaluate are some illustrative cases in this regard. One veteran told me that he had stopped smoking before the War and had no difficulty doing so. He was able to quit 'cold turkey'. While in the Gulf, he began smoking again. Months later, he returned home and tried once more to quit. However, this time he experienced severe withdrawal symptoms and was unable to kick the habit. Did exposures in the Gulf cause him to lose tolerance, leading to addiction in this case? Interestingly, the same veteran also reported having new intolerances for vehicle exhaust, pesticides, bleach, phenolic disinfectants, paint thinner, and perfume with symptoms of lightheadedness, headaches, and nausea; feeling inebriated and stumbling after a small amount of alcohol; and experiencing intense cravings for chocolate, problems he said he had not experienced before the War. Thus, at the same time that he was addicted to nicotine, he was 'abdicted' from other substances.

A number of the Gulf veterans I have seen as a consultant to the Department of Veterans Affairs were regularly consuming ten or more cups of coffee or tea per day, ostensibly to stave off their fatigue. One soldier, who used to drink two pots of coffee a day, said he first suspected that he was sensitive to caffeine when his spouse went away on an trip and he coincidentally stopped drinking coffee for 4 days. He felt 'spacey' and developed a headache. Subsequently, he reduced his intake to two cups of coffee per day.

Now, however, if he drinks more than two cups in a day, he is 'in a state of turmoil', gets 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 just did. This same veteran also said he could no longer tolerate decongestants, diesel exhaust, and certain fragrances, to which he attributes headaches, queasiness, and dizziness.

Another veteran of the Gulf War reported experiencing severe symptoms, reminiscent of caffeine withdrawal, after he was admitted to a psychiatric ward. Only later did he learn that all of the coffee served on the ward was decaffeinated. He also reported headaches after drinking one beer; hypersensitivity to the odor of nail polish or remover; nausea when around cars burning oil; severe weakness, irritability, and headaches if he missed a meal; vomiting after ingesting onions, garlic, or chili; and feeling lightheaded and dizzy if he smoked more than his usual ten cigarettes per day.

About one-fourth of the Gulf War veterans reported that since the War, caffeine made them ill. Most of the others were continuing to use caffeine, but were experiencing insomnia, headaches, irritability, anxiety, palpitations, frequent urination, and other symptoms associated with caffeinism. Yet some of these veterans consumed only a cup or two of coffee per day. Recent, elegant studies have demonstrated that some individuals are sensitive to as little as one cup of coffee per day (Silverman et al., 1992). Have some Gulf War veterans lost their tolerance for caffeine? Removing caffeine from their diets for about a week would help address this question.

Several veterans I evaluated occasionally took decongestant tablets prior to the War without experiencing any difficulty. They described how after the War, when they took the same drugs, they felt 'strung out' for several days afterward, 'wired', 'freaked out', 'hyper', could not get to sleep, or had chest pain. Approximately two-thirds of the veterans reported new alcohol intolerances since the War. They described how a single beer or glass of wine makes them feel inebriated and/or causes a hangover that lasts for several days. Finally, three-quarters of the veterans reported feeling ill after meals or identified new food intolerances, often involving favorites such as pizza and barbecue.

Taken together, these observations suggest that a number of ill Gulf War veterans have lost their prior, natural tolerance for a variety of substances. While one veteran might forestall unpleasant withdrawal symptoms by taking another 'hit', another might avoid the same substance altogether, especially if the latter individual experienced none of the pleasurable effects from exposure/imbibing. Indeed, the same person who avoids one substance might 'abuse' another. The net behavioral effect would be addiction to certain substances and abdiction from others. Arguably, this theory that certain acute high-dose or chronic low-dose chemical exposures cause loss of prior natural tolerance in a subset of the population, leading to addiction or abdiction (Figure 4), is novel.

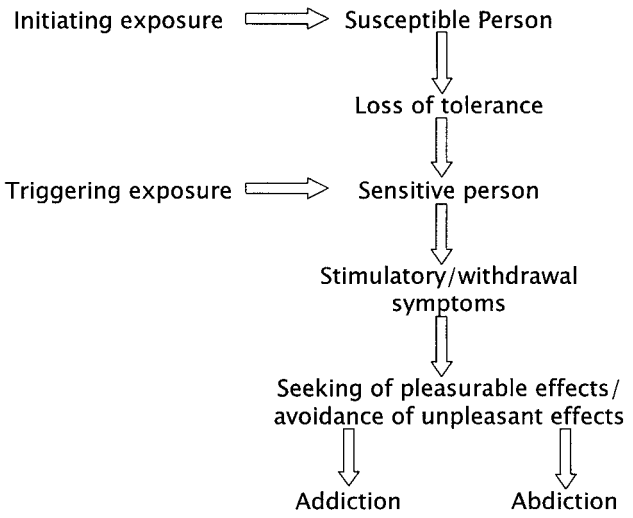

Figure 4. Proposed relationships between TILT, and addiction and abdiction.

In summary, TILT suggests that a wide array of chemical exposures, including air contaminants in sick buildings, solvents, pesticides, and combustion products, can cause certain susceptible individuals to lose their prior natural tolerance for common chemicals, foods, and drugs, resulting in either addictive or abdictive behaviors (or both simultaneously in the same individual) with respect to these substances. Spreading of responses to chemically unrelated substances appears to occur. This theory, founded upon the collective experiences of reliable observers, fulfills the prerequisites of all good theories, i.e., TILT satisfies the four criteria of anomaly, causality, generalizability, and novelty.

Consequences of TILT

What consequences flow from TILT when viewed as a new theory of disease?

Case Definitions

Like the germ theory and the immune theory, TILT describes a *general mechanism* for a class of diseases. The diverse conditions ascribed to TILT (like those ascribed to any other theory of disease) cannot be amassed under the umbrella of any *single* case definition. Both the germ and immune theories of disease encompass multiple syndromes and diverse symptoms involving any and every organ system. Trying to develop a case definition for the TILT class of diseases would be like trying to find a single case definition that would fit all infectious diseases or all

immunological diseases—an impossible task. As an alternative to a case definition for research, we have proposed a series of 0–100 scales that enable subjects to rate the severity of their symptoms and their responses to chemical inhalants, foods, and drugs, and that provide an index of masking (ongoing exposures) that may 'hide' responses to individual substances (Miller and Prihoda, 1998).

Biomarkers

The ability to identify the specific bacteria and viruses that underlie infectious diseases, or the specific antibodies and antigens involved in immunological diseases, did not develop until decades after the germ and immune theories of disease were proposed. Likewise, it may be some time before specific biomarkers for the diseases involving TILT are found. It appears that TILT resembles addiction. Notably, there is no laboratory test for addiction despite longstanding recognition of the problem and decades of research. The only way to diagnose addiction is to stop the substance and observe the organism's response. The same appears true for abdiction. In the future, it is possible that sophisticated imaging techniques, specialized EEG, or brain blood flow measures, especially if conducted before and after withdrawal, and before and after chemical challenges, will offer important new clues concerning the specific mechanisms that underlie addiction and abdiction.

Diagnosis and Treatment

If chemically intolerant persons have multiple intolerances for common chemicals, foods, and drugs, then simultaneous removal of *all* potential triggers should lead to improvement. This thinking underlies recent proposals to establish an EMU, initially for research purposes (Miller, 1997). Without this tool, physicians and researchers lack any systematic, scientific approach for eliminating 'background noise' so that individuals' responses to specific environmental triggers can be tested. An EMU could prove to be as essential a tool for research in this area as the microscope was for the study of infectious diseases.

If TILT results in abdiction (as well as in addiction), then effective drug therapies may elude us for some time. Consider the fact that more than 50 drugs have been tested as potential treatments for cocaine addiction, yet none so far has been found to be effective. Cocaine, a single substance, has been called a 'dirty drug' because it affects so many different types of brain cells, including those involved in the dopamine, serotonin, and norepinephrine neurotransmitter systems. Dopamine alone is associated with five known receptor types. If treating cocaine addiction is so difficult, what about treating health effects resulting from complex chemical environments involving dozens or hundreds of substances, such as mixtures of pesticides, air contaminants in sick buildings, or combustion products? We might expect treating symptoms caused by these exposures to be no less difficult.

In the interim, removal of all potential offending substances, i.e., unmasking, is the most straightforward approach that can be expected to yield the best result. For persons addicted to cocaine, it would make little sense to try to counteract their myriad symptoms with other drugs while they were still taking cocaine. Yet, in effect, this could be what is happening in the case of Gulf War veterans, many of whom report new chemical, food, and drug intolerances, but continue to be exposed to a wide range of potential incitants, perhaps including prescription drugs intended to allay their symptoms (Miller and Prihoda, 1998).

Although substance avoidance is widely accepted as the primary therapy for addiction, the same approach has not been generally recognized for abdiction or chemical intolerance, even though avoidance is the single treatment that most such patients say benefits them most (Miller, 1995; Johnson, 1996; Leroy et al., 1996). Lax and Henneberger (1995) found that chemically intolerant patients who avoided at least half of their self-reported incitants were more likely than non-avoiding patients to report feeling better at follow-up 6 months to 2 1/2 years after their initial visit. Notably, Fukuda et al. (1998) found that one of the risk factors for severe symptoms among ill Gulf War veterans, besides female gender, was smoking. This finding is consistent with the TILT model. If veterans now are intolerant of tobacco smoke, yet continue to smoke, there are no drugs that will eliminate their symptoms. They need to stop smoking. Yet, perhaps because of the severe withdrawal symptoms some now experience when they try to stop smoking or cut back on tobacco use (a possible consequence of their loss of tolerance), it may be especially difficult for them to quit.

Prevention and Public Health

The successful reduction in water-borne enteric diseases in this country was not the result of better antibiotics, but of a preventive intervention—sanitation. Even today, an outbreak of enteric disease remains a signal to us that sanitation practices have failed. Instead of medicating the illnesses that arise from sick buildings or pesticide exposures, a more sensible and economical strategy might be improved sanitation practices, i.e., controlling exposures so people don't get sick in the first place. Societal acceptance of the germ and immune theories of disease paved the way for the implementation of effective preventive strategies. Notably, these strategies became standard practice decades before the specific bacteria or antibodies associated with infectious or immunological diseases were identified. John Snow is credited with having broken the Broad Street pump handle, thus stopping the cholera epidemic in London some *30 years before Koch discovered the bacterium that causes cholera*. As with the germ theory, acceptance of the TILT

theory of disease could propel us toward sound preventive policies and the design of safer products, *even when we do not yet know the specific mechanisms involved and we lack biomarkers*.

What does the future hold? If abdiction/addiction induced by chemical exposures is at the heart of the illnesses we are witnessing, we may be in for a long haul. We have only to look at the public's ambivalence about addiction, the power of vested economic interests (particularly in the environmental health arena), the pervasiveness of psychological explanations, and the complexity of these new concepts—TILT, masking, and abdiction—to gain some sense of the hurdles that lie ahead. At the same time, if chronic and costly conditions like asthma, anxiety, depression, chronic fatigue, migraines, and the illnesses of Gulf War veterans involve TILT, we dare not be complacent about pursuing further research and adopting preventive strategies that respect its rules.

Conclusion

A defining characteristic of science is that it deals in corrigible, tentative statements (Miele, 1998). Like the 'germ' and 'antibody' theories of disease, TILT is a crude, general formulation. The *specific mechanisms* underlying TILT remain to be elucidated. Indeed, at this juncture, it may be important that we *not* specify the underlying mechanism too precisely. While a number of specific mechanistic hypotheses merit our attention (see Ashford and Miller, 1998), we are in urgent need of a more general and less assailable theory that gives meaning to the collective observations by physicians and scientists in more than a dozen countries over the past several decades. TILT is such a general formulation, one that not only offers a new context for our discussions and research, but also suggests sensible, interim measures for the treatment and prevention of a host of chronic and costly illnesses.

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