

Multiple chemical sensitivities or idiopathic environmental intolerances: Psychophysiologic foundation of knowledge for a psychogenic explanation

Publication of two articles in this issue of the *Journal* permits me to revisit a phenomenon that, despite the absence of immunologic abnormalities, has an impact on the fields of allergy and immunology. The phenomenon goes by many names. It was first introduced to allergists in the 1940s as environmental illness (EI) through the writings of the late clinical ecologist, Theron Randolph, and later labeled as multiple chemical sensitivities (MCS) by Cullen.¹ MCS has found its way into our culture as a generic acronym for a myriad of other labels such as environmental illness, universal reactors, chemical sensitivities. Although undefinable, these phenomena share common, multisystem, general malaise complaints that are usually considered debilitating by patients who attribute causation to some external agent (e.g., a virus, foods, chemicals, or electromagnetic forces). Lacking precise definition, these labels are dangerous because they allude to etiologic and mechanistic features associated with other, well-characterized diseases. This type of "validity by association" serves to create an illusion of scientific credibility and suggests an answer to individuals searching for a simple, all-encompassing explanation for their maladies, which does not implicate the self. At its worst, such unsubstantiated postulation harbors iatrogenic exploitation and beliefs of victimization.

Terr² has reviewed the immune theories proposed by clinical ecologists to explain EI or MCS and found them to be unsubstantiated. Salvaggio³ has reviewed immunologic tests and measurements and has shown that they have been misapplied or misrepresented in the context of this phenomenon. There are no valid, scientifically accepted biologic markers that corroborate the hypotheses of clinical ecologists.⁴ Despite the evidence, which includes outright refutation of certain methodologies through double-blind, placebo-controlled studies,⁵ postulation continues unabated. During the past decade, the central nervous system has supplanted the immune system as the most fertile ground for speculation, leading to theories such as limbic kindling, partial limbic

Abbreviations used

DSM IV:	Diagnostic and statistical manual of mental disorders. 4th ed.
EI:	Environmental illness
IEI:	Idiopathic environmental intolerances
IPCS:	International Programme on Chemical Safety
MCS:	Multiple chemical sensitivities

kindling, sensitization, and time-dependent sensitization. These theories have an empiric foundation in the experimental animal literature but lack any established link to ill health effects from low-level chemical exposure in human beings. Furthermore, the hypothesized effects have no specific etiology associated with chemical exposure but can be cognitively mediated as part of the stress response.

Advocates use odor aversion or "cacosmia" as a surrogate for the undefined EI or MCS to speculate on the prevalence of individuals with symptoms. Fifteen percent of the world population is said to meet this crude estimate of prevalence; however, the phenomenon is culturally restricted to North America and Europe, where not a single case has yet been validated in the scientific literature. We should not be too attached to a label that, when subjected to scientific scrutiny, has no relationship to the implied toxicogenic etiology, physiologic mechanisms, or specific symptomatology. This concern was recently addressed in a 1996 MCS Workshop jointly convened in Berlin by agencies of the German government and the International Programme on Chemical Safety (IPCS). Although not acted on by the IPCS Board, and therefore not official policy of IPCS, the recommendations and conclusions of the workshop panel have been published.⁶ One recommendation was to discontinue the use of the label MCS and instead call this phenomenon *idiopathic environmental intolerances* (IEI), thus doing without any implication of chemical etiology or sensitivity mechanisms. The term *IEI* emphasizes that the cause remains unknown. Although there is some resistance to the name change, its value is in its semantic accuracy. This phenomenon may well transcend the moment and have a life as long as one of its well-documented 19th century predecessors, neurasthenia. Lacking an accurate name, we may continually be asked to reconsider the phenomenon anew whenever the

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label is changed, dispensing with the accumulated refuting evidence.

Unsubstantiated theories and misleading labels thrive in a world of irrationality and are judged not only in the scientific community but also in the tort courts and the political arenas of legislation, regulation, and entitlement. The 1993 court decision⁷ that established a new standard for the admissibility of scientific or medical evidence into the federal courts has shifted the tide of expert testimony toward greater scientific credibility, to the extent that testimony based on unsubstantiated or untested theories has been ruled inadmissible in several recent court cases.⁸ The political arena is more tenuous, complicated by allegations of harm, even though no objective evidence of harm exists. An example of this is the Housing and Urban Development project, "Ecology House." Built at a high cost and with extreme care not to exacerbate the symptoms of the EI community who lobbied for it and who participated in the design process, "Ecology House" has satisfied almost none of the tenants and serves only to further exacerbate their feelings of victimization and displaced anger. Despite the political nature of the decision-making processes that seemingly will determine the course of action, the scientific and medical community can best steer this process toward a rational solution through quality research.

Two articles in this issue of the *Journal* enhance our knowledge of how select patients with IEI experience panic responses. The study by Leznoff (pages 438-42) demonstrates objective changes in blood gases characteristic of hyperventilation in response to open exposure to a chemical agent, which had previously been appraised by the subject as being harmful. The study by Binkley and Kutcher (pages 570-4) illustrates how select patients with IEI meet diagnostic criteria for panic disorder and show "reactions" to a triggering agent, lactate infusion, which has been shown to induce panic reactions in patients diagnosed with panic disorder. Indeed, these studies support the psychogenic explanation of IEI. However, we must be cautioned that panic disorder combined with conditioned phobic responses to "chemical triggers," as suggested by Binkley and Kutcher, is neither necessary nor sufficient to explain the many psychologic factors and psychiatric disorders that have been identified in this heterogeneous population. The only unifying psychologic factor among these patients is their overvalued idea that factors in the physical environment are the source of their misery.

We should not be tempted into a simple psychologic explanation for IEI, much less accept that treatment should consist simply of behavioral desensitization. Although, for the sake of parsimony, it may be tempting to think that these reactions are no more than conditioned responses, analogous to Pavlov's dog salivating at the sound of the bell (the conditioned stimulus), which earlier had been rung moments after a piece of meat (the unconditioned stimulus) was offered to the subject. There are indeed well-characterized cases of industrial accidents in which the classical conditioning model may

apply. However, in most cases of IEI, there is no substantiated initial exposure event that would constitute the unconditioned stimulus. Where is the meat? The postulated spreading phenomenon of triggers to any and all chemical products of diverse molecular structure and sensory properties is not only elusive to scientific testing but also defies any known gradient of stimulus generalization characteristic of conditioning. Classical Pavlovian conditioning cannot explain after-the-fact attribution of a triggering chemical, especially if it was not perceived. This is often characterized by the post hoc ergo propter hoc rationalization, "I reacted so I must have been exposed."

Pavlov never intended to explain the complexity of human learning and memory involved in the appraisal and attribution of a "reaction" through classical conditioning. Less known about Pavlov was his interest in a higher order, symbolic form of learning, which he called the second signaling system, or what today is referred to as language and cognition. He succinctly described the central role beliefs have in learned sensitivity, as follows:

Before the appearance of the family of *Homo sapiens* the contact of the animals with the surrounding world was effected solely by means of direct impressions produced by its various agents which acted on the different receptor mechanisms of the animals and were conducted to the corresponding cells of the nervous system. They were the sole signals of the external objects. In the future human beings, there emerged, developed and perfected, signals of the second order, signals of these initial signals, in the shape of speech—spoken, auditory and visible. Ultimately these new signals began to denote everything taken in by human beings directly from the outer, as well as from the inner world; they were used not only in mutual intercourse, but also in self-communication. This predominance of the new signals was conditioned [learned], of course, by the tremendous significance of speech, although words were and remain but second signals of reality. We know, however, that there are large numbers of people who, operating exclusively with words and failing to base themselves on reality, are ready to draw from these words every possible conclusion and all knowledge, and on this basis to direct their own life as well as the life of others.⁹

One finding from double-blind, placebo-controlled studies shows that conditioning alone cannot explain a "chemical reaction." When the unconditioned stimulus (usually an odor) is not detectable because it is either masked by another odor for which the patient shows tolerance or is presented below olfactory and irritant thresholds, the patient still reports having symptoms. It is possible that the patient is responding to other unconditioned stimuli, such as the proprioceptive cues triggered by the alleged toxic agent. Were that the case, subjects should make reliable appraisals of a chemically induced reaction. However, the pattern of responses to active agent and placebo has never been found to be consistent across a series of trials.¹⁰ Selner and I, in a series of unpublished case studies conducted between 1980 and 1985 of subjects sequestered in an environmental care unit with markedly reduced ambient air contam-

inants (which should have freed them from any "masking" effects), found that these subjects were also unable to reliably discriminate a previously identified toxic agent from a placebo control. Another double-blind, placebo-controlled study on intranasal chemoreception in patients with MCS, in which chemosensory event-related potentials were used as an objective measure, demonstrated that 20% of subjects responded regardless of the type of challenge, suggesting that these individuals are susceptible to nonspecific experimental manipulation.¹¹ The psychogenic explanation alternative to conditioning is that subjects respond on the basis of the belief that they have been exposed.

In the *DSM-IV*,¹² panic disorder is classified as one of the anxiety disorders, and for some patients with IEI this diagnosis may be sufficient to explain the symptomatology, as well as the etiology. The triggering effect of lactate infusion in panic disorder has been linked to the central nervous system, as was elegantly demonstrated in a series of proton magnetic resonance spectroscopy brain imaging studies by Dager et al.¹³ Other psychologic disorders noted as typical in patients with IEI include affective disorders and somatoform disorders.¹⁴ The complexity of comorbid *DSM-IV* Axis I diagnoses seems to depend only on the severity of psychologic dysfunction. There is growing recognition within the fields of psychiatry and psychology that Axis I disorders cannot be interpreted without considering individual differences introduced by personality traits and the psychopathology characteristic of personality disorders,¹⁵ which are coded on Axis II of the *DSM-IV*. Specific to this editorial, we must ask the question, "Who is panicking?" Furthermore, patient self-report alone may not be the best way to preclude Axis II considerations.¹⁶

The psychologic picture of IEI is complicated by the finding of a high incidence of premorbid (before the alleged onset exposure) of trauma in patients severely affected by IEI, particularly those who have experienced childhood physical and sexual abuse,¹⁷ which is a replicable finding even in a community sample free of both involvement in tort litigation and iatrogenic influence from clinical ecologists.¹⁸ The long-term sequelae of childhood abuse can have profound effects on mood and affect, cognitive processing, hypervigilance, beliefs and attitudes, personality development and social functioning, and behavior—all of which may be mediated by neurobiologic abnormalities.¹⁹⁻²² In the *DSM-IV* field trials study of posttraumatic stress disorder (which is a typical sequela of long-term and severe childhood abuse), patients were found to have comorbid psychologic disorders including somatization, dissociation, and affect dysregulation, as well as an increased incidence of severe personality disorders.²³ There is growing empiric evidence to support the theory that early interpersonal traumatization gives rise to more complex posttraumatic psychopathology than later interpersonal victimization. Such complexity may be difficult to handle for a nosology such as the *DSM-IV*, which is geared to categorical

diagnosis accompanied by a prioritized sorting-tree approach to differential diagnosis. Nevertheless, it is the comorbid complexity of psychologic disorders that places patients with IEI on the extreme end of the severity continuum.

The two studies in this issue of the *Journal* are pilot studies, a beginning in the verification of psychophysiologically mediated symptomatology associated with panic in patients with IEI. More extensive double-blind, placebo-controlled studies with the lactate infusion method are warranted. Such studies should include a positive placebo control that induces proprioceptive stimulation to test the specificity of lactate in triggering panic. It is possible that patients with IEI will react to any bodily sensation or sensations and amplify the perceived effects into a full-blown panic attack. Objective psychophysiologic measurements and indices of neurobehavioral performance associated with appraisal of a "reaction" should also be included in such studies whenever possible.

Finally, the complexity of the IEI phenomenon and the diverse effects and implications it has on society merit a corresponding amount of attention and research from the academic and clinical scientific communities. Historically, allergists and immunologists have pioneered the use of provocation challenges to establish immunologically mediated allergic and sensitivity reactions and to discriminate among other medical diagnoses and psychologic disorders. These two studies continue that tradition.

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