BY CLAUDIA S. MILLER, M.D., M.S.

Chemical intolerance: Words are everything

Compelling recent evidence suggests that the problem of chemical intolerance is far more serious than scientists previously thought. At the same time, we have discovered that the words and terms we use to describe the overall problem of chemical intolerance and particular associated conditions (such as what we now call MCS) are critical to fostering understanding, acceptance, and medical recognition.

Pivotal medical, compensation, litigation, regulatory, and policy questions rest upon accurately characterizing and understanding chemical intolerance. But the words we currently use are mired in so much misunderstanding that they often impede progress.

This article advances the concept that we are facing an entirely new general class of diseases and that MCS, among other conditions, belongs to this class. It proposes new descriptive words and discusses where we need to go from here.

A NEW CLASS OF DISEASES

The conditions in this new general class of diseases appear to be capable of affecting any and every organ system, and seem to be initiated and triggered by a wide range of exposures. Describing this class accurately is the first essential step toward effective research, regulation, and prevention.

In truth, we are just at the "germ theory" stage in our understanding of chemical intolerance. During the Civil War—only 150 years ago—physicians were baffled by a mysterious "syndrome" characterized by fever. Hundreds of thousands of soldiers died. The doctors then 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 so doing, they unknowingly lumped together dozens of different infectious diseases—everything from typhus and typhoid to malaria and tuberculosis.

IDENTIFYING THE HALLMARK SYMPTOM

Today we face a similar situation. We have defined MCS, fibromyalgia, chronic fatigue syndrome, Gulf War syndrome, and many other relatively recent illnesses, but haven't acknowledged the umbrella hallmark symptom they share. This time the hallmark symptom is not fever, but the newly acquired intolerances these individuals experience, frequently in the wake of one or more chemical exposures—a sick building, pesticide application, solvent exposure, molds, or installation of a medical device such as an implant.

TILT—A NEW THEORY OF DISEASE

What distinguishes these groups is the common experience of an initiating exposure event followed by newly acquired intolerances and multi-system symptoms. These observations, by researchers in more than a dozen industrialized nations, provide compelling scientific evidence for a shared underlying disease mechanism—one involving a fundamental breakdown in natural tolerance. This two-step process—an initiating toxic exposure followed by newly acquired intolerances that trigger multi-system symptoms—is called "Toxicant-Induced Loss of Tolerance (TILT)."

TILT has the earmarks of a new theory of disease. While the germ theory addresses the role of microbes in disease, and the immune theory addresses the role of biological proteins in illness, the TILT theory describes how exposure to certain chemicals (frequently, synthetic organic chemicals) leads to human disease. Just as with the germ theory, the value of the TILT theory lies in its power to enable us to predict that a subset of chemically exposed individuals may emerge with multi-system symptoms and new-onset intolerances for structurally unrelated chemicals, foods, medications, alcoholic beverages, and caffeine, for example.

Understanding TILT helps us predict that *some* of those exposed during the Gulf War or 9/11, or after Hurricane Katrina, will develop multi-system symptoms and new-onset intolerances. Subsequent exposure to various chemicals, foods, drugs, alcoholic beverages, caffeine, and other substances can then trigger a plethora of symptoms. If practitioners and the public can understand TILT, they will then be able to understand why some people continue to be ill even after they leave the war zone or move to a new location.

The fact that researchers have confirmed similar observations of new-onset intolerances and multi-system symptoms following an exposure event in more than a dozen countries is what Kuhn referred to as a "compelling anomaly"—a scientific observation that challenges existing paradigms and calls for the establishment of a new paradigm, in this case a new disease mechanism. TILT does not fit classical definitions of allergy, toxicity, or any other generally understood disease mechanism. That is why this problem has been so difficult for clinicians and researchers to understand and accept.

The same was true for the germ theory of disease. People posited any number of mechanisms to explain the fevers that soldiers and others developed in the late 1800s—most of which were wrong. The germ theory, while it sounds crude today, was in fact what allowed people to take preventive action and undertake productive research. It provided a new, understandable framework for the illnesses everyone was witnessing. Today, TILT has the potential to provide a new, understandable framework for many of the seemingly anomalous illnesses we are seeing—and for their rapid proliferation.

PROPOSED NEW TERMINOLOGY

Why isn't this increasingly common problem of new-onset intolerances and multi-system symptoms apparent to the medical profession? Why don't more doctors see environmental causes as potentially underlying conditions such as asthma, autoimmune diseases, chronic fatigue, Attention Deficit Hyperactivity Disorder (ADHD), autism, fibromyalgia, Gulf War veterans' illnesses, and depression? Much of the blindness and resistance to this possibility is the result of the terminology in common use today, which brings with it the baggage of past prejudices and misunderstandings.

"Multiple chemical sensitivity," in particular, perhaps the most familiar term to us, tends to evoke a negative, knee-jerk response from medical practitioners and researchers. This is in part because allergists co-opted the term *sensitivity* during the early twentieth century to describe an immunological response.

Also, because so many individuals' symptoms were neuropsychological (depression, anxiety, etc.) in nature, their illnesses were assumed to be psychogenic—mental or emotional in origin, as opposed to physiologic. Affected individuals were either dismissed or referred to psychiatrists for treatment, and their problems treated accordingly. This is the unfortunate history of this area, extending back to the early 1950's when allergist Theron Randolph first called attention to the problem.

The most important factor that has made the MCS disease process elusive is the phenomenon known as "masking." A masked individual is subject to multiple environmental exposures, which can make the person's specific sensitivities nearly impossible to detect (until he or she is isolated and returned to a baseline state, or "unmasked"). The effects, and the symptoms, become blurred. For example, the patient in a large city may be exposed intermittently to a wide range of potential irritants such as car exhaust, perfumes, pesticides, various foods, volatile chemicals off-gassing in building spaces, and more. In that individual, overlapping or successive exposures result in overlapping symptoms. Masking hides the relationship between symptoms and exposures. Trying to recognize individual triggers in a masked individual is like trying to hear a pin drop in a noisy room. There is simply too much background noise.

What can be done? First, the term *chemical sensitivity,* or *multiple chemical sensitivity*, continues to pose major difficulties to practitioners and to the public. *Intolerance*, on the other hand, is a term that is easily understood and accepted (including by allergists) and translates meaningfully to other languages. It is a term that will not go out of date or be challenged, as *sensitivity* has been.

The disease theory called TILT, summarizes simply, and without bias toward any particular explanation or mechanism, what has been observed worldwide. In the future we are likely to learn that TILT can involve many different specific mechanisms, just as various bacteria, viruses, rickettsia, and other infectious agents can cause illness and fever by differing mechanisms, affecting different organ systems. Exactly how pesticides, sick buildings, and implants initiate TILT may differ, but the resulting illnesses would nonetheless fall in the TILT class of diseases.

I have written and talked about this concept for more than a decade. In my experience, no scientist wishes to deny that we may in fact be witnessing the emergence of a new class of diseases, paralleling the discovery of infectious or immunological diseases.

Starting with TILT as the basic theory, we could apply it to what we currently label MCS by calling the combination of multi-system symptoms and multiple intolerances that affected individuals report, *multiple chemical intolerance*. Again, I see chemical

intolerance as the hallmark symptom of this new class of diseases, just as fevers are the hallmark symptom for infectious diseases.

JUST SAY NO TO A CASE DEFINITION

Given the above, it does not make sense to me to try to develop a case definition for this new class of diseases. It would be like trying to develop a single case definition that would cover all infectious diseases. There can be case definitions for particular infectious diseases, but no one definition can encompass all of them. Until we are clear about this, it will be difficult for researchers to take up this cause. If we are clear about it, then the symptom of chemical intolerance becomes the hallmark for a new class of diseases. This establishes a framework for future research, and informs medical professionals that they need to look for TILT in a vast array of chronic medical conditions whose prevalence is on the rise in this country and abroad.

For research purposes, an environmentally controlled hospital unit is an essential tool for unmasking patients and demonstrating the role of exposures in chronic illnesses. Randolph himself said that without an environmentally controlled hospital unit, he would never have understood this problem, which he variously referred to as "chemical susceptibility" or "the petrochemical problem." He also said that such units were essential for other doctors to understand the problem—they must see the responses firsthand.

We are in desperate need of environmentally controlled hospital units, or Environmental Medical Units (EMUs), none of which currently exist in the United States. We could begin by evaluating 30 patients with asthma or 30 with lupus, 30 ill Gulf War veterans or 30 children with autism, and determining how many of their conditions resolve or improve as a result of isolating them from environmental exposures. Restricting ourselves to a narrow case definition (one that might not apply to these groups prior to unmasking) reduces the focus for research and diagnosis to a much smaller number of individuals—those who already are aware of their chemical intolerances.

We are facing an entirely new general class of diseases...conditions... [that] appear to be capable of affecting any and every organ system and seem to be initiated and triggered by a wide range of exposures.

What if the germ theory had been limited to a specific group of symptoms? That would not have worked. It is fine to talk about chemical intolerance as a hallmark symptom for a class of conditions that appear to be environmentally initiated and triggered. But we must not limit our studies to a particular subset of symptoms and in the process exclude other TILT-related conditions. If the germ theory had been limited to fever, coughing, and rashes, think how much we would have missed.

During the last century, allergists redefined their field in terms of IgE-mediated disease (in which the antibody IgE is produced by the immune system in response to an exposure, leading to allergic symptoms), thereby excluding individuals who suffered from adverse responses to drugs, foods, and chemicals that were *not* IgE-mediated. That single act led to the difficulties and confusion we face today, which have resulted in suboptimal care, or no care, for many patients. We must not repeat this error now by "defining out" (i.e., excluding from study) conditions that involve multiple chemical intolerances.

PERHAPS THERE IS A MIDDLE GROUND

Despite the misgivings I've expressed, researchers need case definitions, and they will choose their own based upon what they are investigating. Definitions may be needed for treatment and compensation. I am not opposed to saying something to the effect that people who: (a) exhibit multiple intolerances to a wide variety of substances (structurally unrelated chemicals, and often various foods, medications, alcoholic beverages, and caffeine) and (b) have symptoms resulting from these exposures (the symptoms may involve one, but more typically multiple, organ systems) are suffering from *multiple chemical intolerances* (MCI). Symptoms can range from mild to disabling and frequently require major lifestyle changes.

MCI is not a syndrome. A "syndrome" is a constellation of symptoms that is associated with a particular disease. Here, we are dealing with multiple diseases, not just one, so we must not call this a syndrome. Adding the word "syndrome" may sound more official or important, but in fact it only increases the resistance to this problem by researchers and practitioners. MCI is more akin to "fever," which we now know as a hallmark symptom for infectious diseases. Likewise, as we've seen, intolerances are the hallmark symptom for TILT. Those affected by TILT suffer from MCI. On the other hand, not all MCI patients may have had an initiating chemical exposure—or at least not one that they recall. The terminology proposed here takes care of this problem.

QEESI AIDS RESEARCHERS

Because of the difficulties inherent in conducting research in this area without a definition for multiple chemical intolerance, my colleagues and I developed a questionnaire, the Quick Environmental Exposure and Sensitivity Inventory (QEESI), which embodies the major dimensions of this problem. It enables researchers and

clinicians to characterize patients by the intensity of their intolerances and the severity of their symptoms. The QEESI is distilled from data collected from hundreds of patients who have multiple chemical intolerances in a variety of settings. The five scales of QEESI gauge: (1) the severity of responses to 10 different, everyday chemical exposures, (2) responses to 10 other common exposures including foods, medications, alcoholic beverages, and caffeine, (3) symptom severity, (4) masking, and (5) life impact or disability.

At a minimum, these five key dimensions of MCI need to be assessed in every research study and by every clinician who sees patients. Even doctors or medical students who know nothing about this problem find they are able to ask the right questions if they use this questionnaire. The Japanese government used the QEESI in a national prevalence study, and investigators in other countries are currently using it in their studies. Without such a uniform measure, it would be impossible to know whether the individuals seen by one group of practitioners, such as allergists, were in fact comparable to those seen by occupational-medicine specialists or some other group of practitioners, or to assess differences between populations in the U.S. and other countries.

The QEESI is meant to supplement, not supplant, practitioners' own evaluations or questionnaires. Sick-building investigators are providing the QEESI to occupants so that those occupants can get an idea of their own relative susceptibility to indoor exposures. This approach reinforces the concept of individual differences and the need to accommodate more susceptible individuals in the workplace or in schools. Researchers are using the QEESI to evaluate potential changes in symptoms and intolerances before and after chemotherapy, and before and after various treatment regimens. Whatever the treatment or treatments—avoidance of exposure, dietary changes, vitamins, medications, detoxification, psychological support, or something else—the QEESI allows clinicians and investigators to measure the impact of their treatment at intervals. Because the QEESI is validated and published, results from even small solo medical practices are potentially publishable. A major advantage is that the rating process is done by those who are ill. They rate their own symptoms and intolerances rather than our having to rely on their physician's assessment of the situation.

My recommendation is to invoke and investigate the TILT disease mechanism whenever an exposure appears to have initiated the multiple intolerances. We should insist that government and university researchers add the QEESI to their research on other affected

PROPOSED DEFINITIONS

Multiple Chemical Intolerance (MCI): A symptom complex characterized by multiple intolerances to a wide variety of substances (structurally unrelated chemicals and often various foods, medications, alcoholic beverages, and caffeine) with symptoms triggered by these exposures. Symptoms may involve one, but more commonly multiple organ systems, and can range from mild to disabling. Avoidance of symptom triggers may necessitate major lifestyle changes. Tiny amounts of substances that most people tolerate, and that the affected individual tolerated previously, trigger symptoms. Intolerances may increase and "spread" to encompass an increasingly broad range of chemicals and foods.

Masking: Multiple, overlapping symptoms triggered by everyday exposures. Masking hides the relationship between symptoms and specific triggers, making it difficult for those who are ill and for their physicians to diagnose MCI.

Toxicant-Induced Loss of Tolerance (TILT): The underlying disease process that results when an occurrence of chemical intolerance (MCI) follows an identifiable exposure or series of exposures, such as a pesticide application, indoor air pollutants, solvents, or other acute or chronic chemical exposures. Evidence for this disease mechanism comes from observations by physicians and researchers in more than a dozen countries. TILT appears to involve two steps:

1. Initiation, or the loss of prior, natural (innate) tolerance following a single, high-level chemical exposure such as a chemical spill, or repeated low-level exposures such as air contaminants associated with new construction. TILT may result from one or more exposures occurring simultaneously or sequentially over a period of weeks, months, or longer.
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 affected individuals report a reproducible constellation of symptoms, or signature response, following each exposure to a particular trigger (for example, headaches with diesel exhaust or cognitive difficulties with a fragrance).

groups—for example, Gulf War veterans, those with autoimmune disorders, post-9/11 and Hurricane Katrina victims, and others. Only in this way will other scientists begin to see for themselves the extent to which chemical exposures may have initiated or be triggering these conditions.

THE RIGHT WORDS CAN PAVE THE WAY

Until we get the words right, this compelling anomaly may never receive the attention it deserves, and the very real suffering TILT explains may never be appropriately addressed and alleviated. Adopting the proper terminology will help to reshape the mindset of practitioners and the public alike. Research tools such as Environmental Medical Units and the QEESI are ready to be applied to advance our knowledge of this largely unseen, unrecognized problem. Once we agree on what to call these things, perhaps then we will be able to offer new hope to people who desperately need it, and new insights and directions for research into many of our most common diseases.

Claudia S. Miller, M.D., M.S., is a tenured professor and assistant dean at the University of Texas School of Medicine in San Antonio, TX. She is board-certified in allergy/immunology and internal medicine, and is a former industrial hygienist. She and Nicholas Ashford, Ph.D., J.D., of MIT, co-authored the landmark New Jersey Report on Chemical Sensitivity (for which New Jersey received the WHO Macedo Award), and the book Chemical Exposures: Low Levels and High Stakes *(2nd ed., Wiley). She led two NIEHS/NIH meetings on TILT and the need for Environmental Medical Units, has published numerous papers on TILT, and has served as a consultant to the EPA, ATSDR, NIEHS, and other state and federal agencies, as well as the governments of Canada, Germany, Sweden, Thailand, and Japan. MillerCS@uthscsa.edu.*