



Claudia Miller, MD

An Emerging Paradigm: Chemical Exposures and Health

Interview by Bonnie J. Horrigan | Photography by Bob Werre

Claudia Miller, MD, is professor, vice chair for Community Medicine, and director of the South Texas Environmental Education and Research (STEER) program at the University of Texas Health Science Center at San Antonio (UTHSCSA). Board certified in internal medicine and allergy-immunology, she completed her medical and fellowship training at UTHSCSA and her residency at Brackenridge Hospital in Austin, Texas. In addition, Miller holds a master's degree in environmental health from the University of California-Berkeley School of Public Health.

Miller's research interests include occupational and environmental health, chemical intolerance, indoor air pollution, health effects of low-level chemical exposures, neurotoxicology, limbic sensitization, and cholinergic sensitivity. She specifically focuses on the role low-level chemical exposures play in a wide variety of illnesses, including asthma, autism spectrum disorders, attention deficit hyperactivity disorder, headaches, chronic fatigue, fibromyalgia, and depression, as well as "Gulf War Syndrome" and implant-related illnesses.

She has held appointments on several national scientific panels—the Department of

Veterans Affairs Persian Gulf Expert Scientific Committee, the National Toxicology Board of Scientific Counselors, and the National Advisory Committee on Occupational Safety and Health.

Along with Nicholas Ashford, PhD, JD, of MIT, she coauthored the book *Chemical Exposures: Low Levels and High Stakes* and the landmark *New Jersey Report on Chemical Sensitivity*, for which the New Jersey Department of Health received the World Health Organization's prestigious Macedo Award. She also organized and chaired two groundbreaking National Institutes of Health (NIH) meetings: the first, a gathering of physicians and scientists to examine the use of environmentally controlled hospital facilities for research and, the second, a conference jointly sponsored by the National Institute of Environmental Health Sciences (NIEHS/NIH) and the National Institute on Alcohol Abuse and Alcoholism (NIAAA/NIH) concerning a new disease mechanism she first described, called *toxicant-induced loss of tolerance*.

EXPLORE interviewed Dr. Miller at UTHSCSA in San Antonio, Texas, in the spring of 2006.

EXPLORE: Let's start with how you came to the toxicant-induced loss of tolerance (TILT) theory. Did you begin with environmental studies or the study of addiction?

CLAUDIA MILLER: I began my career as an industrial hygienist, as a person who studies exposures and tries to protect people from getting sick in the workplace. In the late 1970s, I was asked to investigate several outbreaks of illness in manufactur-

ing plants where people were making circuit boards. Most of the employees were women. They were reporting headaches, fatigue, and nausea and a whole series of what doctors call "subjective symptoms." The National Institute for Occupational Safety and Health (NIOSH/CDC) also sent in investigators. At the time, they were calling this "mass psychogenic illness."

EXPLORE: Oh, dear.

Claudia Miller, MD, shown here under a tree on the UTHSCSA campus, has focused her research on issues surrounding the health effects of chemical exposures.

MILLER: Yes, this was before we knew about sick buildings. The outbreaks were occurring at times of peak production when solder fume exposure was at its highest. The problem was that there was no local exhaust ventilation for these activities and no fresh makeup air being added to the mix. Today, we would call this a sick building. But back then they were calling it mass psychogenic illness.

We noticed that not everyone who worked in these plants developed problems; some people appeared to be more susceptible than others. Unfortunately, people who are less susceptible sometimes dismiss the concerns of those who are more susceptible and treat them as if there were something wrong with them psychologically. These plants eventually did make corrections, and the health problems resolved, but, over time, we saw many more outbreaks of sick building syndrome, including, ironically, in the EPA's own headquarters.

The EPA headquarters building in Washington, DC, was an older building that had been converted into office space. About 50 HVAC (heating, ventilation, and air-conditioning) units were on the roof. Some were bringing in very little fresh outside air. In 1987 and 1988, contractors installed 27,000 square yards of new carpeting. Portions were glued down. From a national perspective, off gassing of chemicals from carpets has since been reduced in a cooperative agreement between the EPA and carpet manufacturers, but, back then, the emissions were quite high, and the odor was very strong. In addition, they also repainted the offices. So, between the lack of fresh makeup air and several strong sources of chemicals being emitted inside the building, people who were sensitive started having health problems.

By off gassing, I mean that materials—carpet, building materials, particle board, furnishings—are releasing low levels of volatile organic chemicals (VOCs). If you compare an air sample taken inside a sick building to the air outside using gas chromatography, you can see the number and concentrations of these volatile organic chemicals. There are far more chemicals and at higher concentrations indoors than outdoors. It wasn't like this in the past. But now, in office buildings, homes, schools,

stores, churches, you will find hundreds of VOCs emanating from products, wall treatments, and construction materials that didn't exist a few generations ago.

I decided to go to medical school because I wanted to work on this problem and how it might be related to chronic health conditions—illnesses that are costly to patients and society and seem to be increasing in prevalence. I had planned to go into private practice, but, when I realized that there wasn't enough basic scientific information yet, I chose to do research.

EXPLORE: Who sets the architectural standards for fresh air in buildings? How does that work?

MILLER: The American Society of Heating, Refrigeration and Air Conditioning Engineers (ASHRAE) sets these standards now. Recently, I was appointed to serve on the ASHRAE panel on environmental health, so I now hope to be part of this process. To me, this is one of the most important contributions I can make. I can do research, and I can see people who are sick, but I can't help them if they are in a building or home that doesn't have enough fresh air.

When ventilation standards were set back in the early 1900s, the fresh air requirement was 30 cubic feet per minute per person in a space when it was maximally occupied. It was set that high because, back then, people didn't take a lot of baths and the odor of a group of people in a room could be offensive. Later, the standard was revised downward, to 10 cubic feet per minute per person, when indoor plumbing became available and people started bathing more. Then in the mid-1970s, the standard was further decreased to five cubic feet of fresh air per minute per person, one sixth of what it had been! That was the time of the first oil embargo, and the nation was trying to save energy. This may sound like a lot of engineering, but it is important for doctors to understand all of this because this is why we are having such difficulties now.

We started seeing outbreaks of sick buildings across the country when the ventilation standard was reduced to this low level. Unfortunately, about one third of the buildings in this country have been built to that standard.

A recurring question has been: why do some people get sick in a building while others do not? There is a tendency to think that there must be something inherently wrong with the people who become ill. Maybe they recently experienced some trauma, or they are having difficulties at home. This frustrates me. I am speaking next week at the American Psychiatric Association's national meeting and have titled my presentation "Environmental Psychiatry: From Sick Buildings to the Gulf War." The focus will be on how exposures affect cognition and mood and what the relationship is between exposures and conditions such as ADHD, autism, and bipolar illness. People don't think of these problems as potentially being environmental in origin. Patients can have psychiatric symptoms, but that does not mean their symptoms are psychogenic.

More than 50 years ago, a Chicago allergist named Theron Randolph described the first case of multiple chemical intolerance. The patient was a physician's wife who sold cosmetics. She reported feeling ill whenever she drove through heavily industrialized areas. Other exposures that provoked her symptoms included exhaust in train stations, perfumes, and cleaning agents. Randolph referred to this phenomenon as chemical susceptibility or the "petrochemical problem." Over several decades following World War II, he and his colleagues observed that chemical exposures appeared to trigger fatigue, migraine headaches, arthralgias, asthma, and other chronic health problems in increasing numbers of patients.

When I work with patients, I always ask which pesticides and cleaning agents they are using and what kinds of building materials are in their homes. In fact, I can tell more about a patient by visiting his or her home than I can by talking to that person. Most doctors don't take an exposure history, but they need to because chemical exposures may be the underlying cause for so many chronic conditions. We have published a validated screening questionnaire called the Quick Environmental Exposure and Sensitivity Inventory (QEESI) that helps doctors ask key questions (*Toxicology and Industrial Health* 1999;15:370-397).

EXPLORE: I understand you have an elective for medical students that teaches about environmental exposures.

MILLER: That's right. I direct the South Texas Environmental Education and Research (STEER) center, which offers a one-month elective for medical, public health, and other health professions students. The focus is environmental medicine. We take them to the homes of children with asthma to identify exposures that may be contributing to asthma. We assist the families with practical, personalized control measures, whether it's putting dust mite-resistant coverings on the mattresses and pillows or curtailing the use of candles or fragrances indoors. Our program takes place in Laredo, Texas, at the US-Mexico border, where the use of candles is prevalent. In fact, if you have a sick child, you may be more likely to use religious candles and more of them, yet they generate large amounts of very tiny particles that are irritating to the lungs. Irritation causes inflammation, and inflammation is what we treat when we are treating asthma. In these homes, we strive to reduce or eliminate potential contributory exposures.

We do everything we can to make our teaching experiential and memorable—from looking at live dust mites under a microscope to measuring the particles coming off of a candle to going into the field and tasting some of the medicinal herbs that are commonly used here. We also have the students buy a month's worth of groceries in Nuevo Laredo for a family of four using a week's worth of wages (about \$40 US), so they understand the expense and the nutrition challenge families face. They see outhouses, dirt floors, and makeshift houses in which an entire family uses one twin bed. Many families don't have running water. Their water may be stored in 55-gallon drums that formerly held chemicals. It's an eye-opener for the students.

If we can teach the next generation of health professionals about the importance of their patients' personal environments, then they will learn to ask whether pesticides are being used and whether there is any new construction at home or at work. Those are key questions. If a patient says that he is better when he's away from his office or away from home on vacation,



When she isn't working, Dr. Miller relaxes by dancing the tango, a social dance form that originated in Buenos Aires, Argentina.

then his doctor should have a high index of suspicion. If doctors don't think of potential environmental causes, they will never make the diagnosis. Physicians who understand this can help their patients avoid these exposures. Asking patients to deliberately avoid a suspect environment or exposure for a week or two can be very revealing if they chart the severity of their symptoms. The QEESI can be useful for this.

EXPLORE: You mentioned that there are more chemicals in our environment than ever before.

MILLER: Several generations ago, our exposures were very different. We didn't have all these synthetic organic chemicals. Since World War II, there has been an exponential increase in the production and use of synthetic organic chemicals—everything from solvents to pesticides to cleaning agents—that have

found their way into our indoor environments, which are now tightly sealed. Once we recognized that lack of fresh air was a major factor in sick buildings, the ventilation standards were changed. But only in the last 10 years have the requirements been increased to 15 to 20 cubic feet per minute per occupant.

Think about what we do to get our homes ready for a new baby. We cover the floor with soft, padded carpeting because the child will be crawling on the floor. We paint the nursery, get a new bed, and often that and the drawers of the new matching dresser are made with particleboard, which off gasses formaldehyde and other VOCs. Clothing or bedding placed in those drawers absorbs these VOCs and, later, reemits them in the breathing zone of the child who wears that clothing or lies on those sheets. We purchase a new plastic-covered mattress. We use scented fabric softeners. And, since we don't want bugs crawling around on the floor, we exterminate the house. Then, to cover any odors, we plug in or spray air fresheners or deodorizers. In doing these things, we are exposing infants and children to numerous chemicals while their brains are still developing. This is what makes me so concerned about ADHD and autism. How do these early exposures affect the formation of critical synapses in the brain?

I want to talk about mold for a moment. If materials like carpet or wallpaper get wet, then, in 48 to 72 hours, mold will start to grow. This is a huge problem in humid regions, but it is also a problem when pipes leak or after floods or hurricanes. Mold grows on anything organic. The walls of our buildings are now made of sheetrock, which has cardboard on each side. There are mold spores already present in the sheetrock, and, if they get wet, the spores germinate and mold grows. Molds release VOCs, called *mVOCs*, which are esoteric organic compounds, some of which help the molds compete in the environment. So it isn't just that molds and mold spores trigger allergies, but molds can emit *mVOCs* that cause problems for chemically susceptible individuals. Some molds also produce toxins.

“The most sensitive people are the canaries in the coal mine, and we need to listen to them because they are protecting the rest of us.”

Often when there is a building-related exposure, a mold problem, or other chemical exposure, only one or two individuals report problems. They may be the most sensitive people. We must listen to them. They are the canaries in the coal mine. We need to listen because they are protecting the rest of us, and, if we can address their concerns and fix the source of the problem, we are apt to protect everyone, including pregnant women, children, and the elderly.

EXPLORE: Why are some people more sensitive? Do we know?

MILLER: There are several theories. Paradoxically, interest in environmental exposures has increased as a result of the Human Genome Project. We are starting to grasp the extent to which people differ in their response to toxic chemicals. Dr. Samuel Wilson, deputy director of NIEHS, coined the term “toxicogenomics” to describe this emerging new field. For example, the gene PON1 is involved in producing an enzyme that detoxifies organophosphate pesticides. People differ tremendously in their ability to do that. The structures of our PON1 genes vary. It's not that there is something wrong with people who can't detoxify these substances. There is a wide range of normal genetic variation that determines PON1 function. Rather, it's our exposures to organophosphate pesticides since World War II that have brought attention to these differences. The same can be said for many other synthetic organic chemicals. So that now, in the 21st Century, being less able to detoxify certain substances may actually be a handicap. These expo-

sure were not a concern in our great-grandparents' day. Humans simply do not have the capacity to detoxify or eliminate all of the synthetic substances that have entered our environment over the past 50 to 60 years. Our genes really haven't changed during that time. Evolution takes eons.

Regarding genetic differences that may underlie toxicant-induced loss of tolerance, one of the most exciting developments reported at the NIH conference on addiction and chemical intolerance was a Canadian study of women who reported multiple chemical intolerances. One reason this problem has been dismissed in the past is that no one could believe it was possible for people to respond adversely to such low levels of so many structurally unrelated substances. In allergy, that certain doesn't fit the usual pattern. If you are allergic to cats, it doesn't mean that you will be allergic to peanuts and penicillin too. Allergies are highly specific—we develop antibodies to specific exposures, to specific allergens. Nor did chemical intolerance fit the tenets of toxicology. The levels of exposure leading to symptoms were far lower than those generally recognized as toxic.

So chemical intolerance didn't fit any known categories of illness. It certainly didn't fit what we learned in medical school. How could people be reacting adversely to low levels of pesticides and fragrances and diesel exhaust, not to mention foods and food additives? We knew there weren't measurable antibodies present in most cases, and the levels of exposure that triggered symptoms were far below those the OSHA or the EPA considers toxic.

McKeown-Eyssen and colleagues (*International Journal of Epidemiology* 2004;33: 971-978) compared 200 Canadian women reporting chemical intolerances with women who were not chemically intolerant. They studied selected genes in the two groups and found that the chemically intolerant women were two to four times more likely to have particular genetic polymorphisms (variations) than the controls. For instance, the gene CYP2D6 is essential for the metabolism and detoxification of many commonly prescribed, structurally diverse drugs, such as various antidepressants, codeine, and amphetamine, as well as a host of environmental chemicals. Its polymorphisms determine

our ability to detoxify these substances. Even tiny variations can result in the coding of detoxification enzymes that differ greatly in their structure and activity. Other researchers have linked certain PON1 polymorphisms to illness among Gulf War veterans who reported becoming sick following an organophosphate nerve agent exposure. The capacity of two individuals to detoxify a pollutant can differ by several orders of magnitude. To me, this says that we need to focus on minimizing potential problem exposures because we cannot change our genes and we currently cannot predict who will respond adversely to which chemicals.

My work has focused on why, after an exposure event like a sick building episode or a pesticide application, a subset of those exposed go on to develop multisystem symptoms and multiple intolerances. This is a worldwide phenomenon, one that has been reported by researchers in more than a dozen countries. Our book, *Chemical Exposures: Low Levels and High Stakes*, has doubled in size since the first edition because there have been so many more reports of sick buildings, pesticide exposures, and similar health problems among Gulf War veterans and implant patients.

At first, I had no idea that there might be some individuals who were more susceptible than others to certain implant materials, but this may be why some but not all women report health problems following breast implants. If you look at epidemiological studies, you may not see an increase in definable autoimmune diseases like lupus among these women. Instead, there appears to be a spectrum of symptoms, which differ from person to person depending upon their genetic makeup and sensitivities, but the symptoms rarely add up to a diagnosable autoimmune disease. I was surprised to find that both the Gulf War veterans I saw as a consultant to the Department of Veterans Affairs and the women we studied who reported illness after implantation seemed to share something in common. Both of these groups, like the sick building occupants and pesticide-exposed individuals we had studied previously, reported multisystem symptoms and chemical, food, and drug intolerances that surfaced after their exposures. People's responses to chemical exposures are so diverse that, even individuals who were side by side in

the same sick building or the same war, and had similar exposures, manifest differently.

All science begins with observation, and researchers and scientists in over a dozen industrialized nations are seeing the same thing we are seeing. After an exposure event, a group of people, not just one person but a group, may become ill. The fact that these episodes are occurring in different countries where people don't speak the same language, don't read the same books, and don't watch the same TV shows is compelling evidence that there is something new going on, something we don't yet fully understand.

“It's the ‘compelling anomaly’ that exposes the limitations of existing paradigms and thereby drives the search for a new paradigm.”

When Thomas Kuhn wrote *The Structure of Scientific Revolutions*, he explained how new paradigms emerge in science. He said that it's the “compelling anomaly” that exposes the limitations of existing paradigms and drives the search for a new paradigm. The compelling anomaly in this case is the reporting of chemical, food, and drug intolerances and multisystem symptoms among diverse groups who share one thing in common—a prior exposure event. These observations do not fit our current understanding of allergy or toxicology. So something else must be going on.

What might explain these observations? There are some intriguing clues. Interestingly, adults who become chemically intolerant often report becoming easily inebriated or suffering severe withdrawal symptoms after only one beer or a glass of wine. Thereafter, they avoid it.

EXPLORE: That's interesting. I have a friend who recently told me that, all of a

sudden, she can no longer drink white wine. It makes her sick.

MILLER: When I hear that from an adult who used to be able to drink, then I want to ask, has your health changed, has anything changed in your home environment or your work environment? Do you use pesticides? Has there been any new construction or remodeling? To me, a sudden loss of tolerance for alcohol is the single most important clue in an adult that something may be going on. We saw it in many Gulf War veterans. Soon after the first Gulf War, the Department of Veterans Affairs flew me down to Houston to take occupational and environmental histories on dozens of Gulf War veterans referred there. While I was seeing them, I also collected information about any new intolerances they might have and discovered that they were saying the same things that people who had become ill in sick buildings or after pesticide exposures had said. They could no longer tolerate particular foods, food additives, chemicals, medications, alcoholic beverages, or caffeine.

When people travel, or have an upcoming exam or simply a lot to do, it is normal to feel tired. So what do we do? We seek out mild stimulants such as carbohydrates or caffeine to give us a lift. But there can be withdrawal effects afterward. The people who experience withdrawal—this is a key item on our screening questionnaire for chemical intolerance—are more likely to be individuals who are sensitive to other exposures. So caffeine, alcohol, chemical, food, and medication intolerances seem to occur together in the same individual. That's another important clue.

EXPLORE: Let's talk about the TILT theory and the relationship between addiction and chemical intolerance.

MILLER: After a major exposure event such as a sick building, a pesticide application, or the Gulf War, only a subset of people develops these intolerances. We call this process “toxicant-induced loss of tolerance” or TILT. It appears to evolve in two stages. The first is initiation, characterized by a profound breakdown in prior natural tolerance resulting from either acute, high-level or chronic, low-level exposure to chemicals. This is followed by the triggering of symptoms by small quantities of previously tolerated chemicals, foods, food additives, medications, caf-

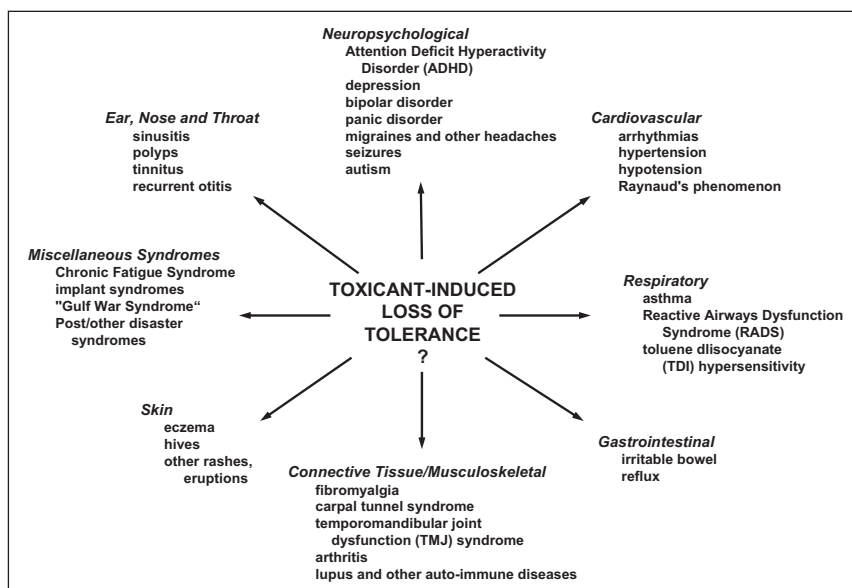
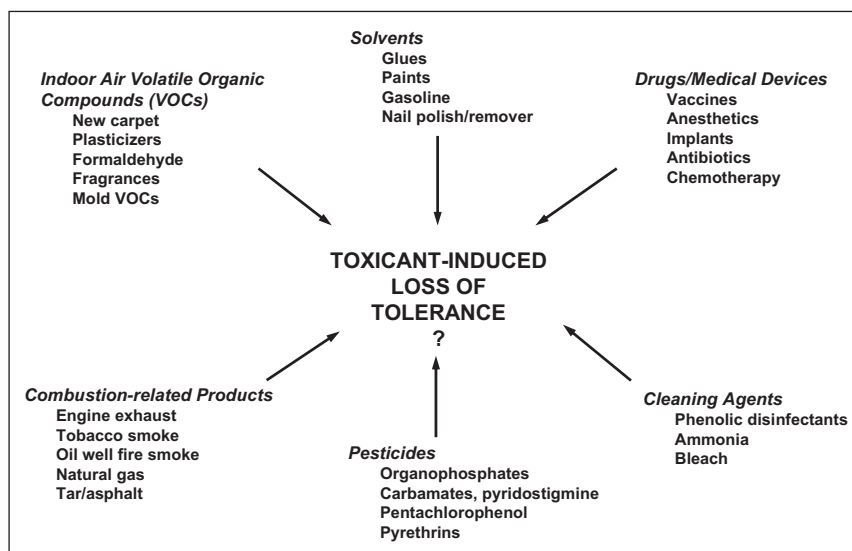


Figure 1. Toxicant-induced Loss of Tolerance Triggers and Symptoms.

The opposite is addiction—here the person starts to go through withdrawal and wishes to avoid it, so he takes another hit. This cycle repeats itself, so the person continues to take carefully timed hits throughout the day. Caffeine, tobacco, foods, anything that people may be sensitive to—in order to avoid withdrawal symptoms, they take another hit and keep themselves titrated. So addiction and abidction appear to be related behaviors, mirror images of each other. Both involve cravings, and both are successful strategies to avoid unpleasant withdrawal symptoms.

The idea that these phenomena could be related and occur simultaneously in an individual dawned on me when I was interviewing the Gulf War veterans. A veteran would be telling me that he was now drinking 10 or more cups of regular coffee a day. At the same time, he was avoiding solvents he had previously worked with as a mechanic and avoiding alcohol because of severe withdrawal symptoms. I couldn't understand it. Why would this person simultaneously be avoiding alcohol and abusing caffeine? Interestingly, alcohol is something people tend to consume on weekends or sporadically. Consequently, they are more likely to notice the stimulatory and withdrawal symptoms associated with its use than they are with caffeine. People tend to use caffeine every day or several times a day. We say they are "masked." Masking occurs when the effects of exposures overlap in time and people cannot tell what is causing their headaches, fatigue, or other symptoms. It is a little like trying to hear a pin drop in a noisy room. There is too much background noise resulting from overlapping responses to multiple exposures. One would have to stop all caffeine and other relevant exposures for a while—get to a clean baseline—in order to figure out which exposures were triggering which symptoms.

There is important new work going on at the National Institute on Drug Abuse (NIDA/NIH) related to food addiction. Dr. Nora D. Volkow, director of NIDA, has been using brain imaging to study how the brain responds to certain foods and is interested in how food addiction might contribute to obesity. In my experience, the most common food addictants are corn, wheat, milk, and eggs. These also put on the pounds. A question that intrigues me is

feine, or alcoholic beverages. No one understands the mechanism yet, but the result is that these people begin to experience stimulatory and withdrawal symptoms that can be very unpleasant, even disabling. When this occurs, then, consciously or unconsciously, these individuals go in one of two directions—addiction (craving) or abidction (aversion).

When people develop augmented stimulatory and withdrawal responses, they generally try to avoid the withdrawal symptoms. They can do this either by "taking another hit" or by avoiding the substance altogether. Take caffeine. It can

produce a rush that makes some people feel uncomfortable and jittery, but, usually, the bigger problem is the withdrawal, which may be accompanied by headaches, fatigue, irritability, and difficulty concentrating. Most people want to avoid these unpleasant withdrawal symptoms.

There are two ways to do this. First, if they know their symptoms are due to caffeine, then they can avoid it, and after a week or two, their withdrawal symptoms will cease. No further problem occurs as long as they avoid caffeine. This is what we call abidction, which is avoiding or moving away from the substance.

whether overeating could be due to food addiction brought on by exposure to environmental toxicants—toxicant-induced loss of tolerance. Is it possible that everyday exposures to indoor air pollutants, pesticides, traffic exhaust, fragrances, and other contaminants have something to do with our obesity epidemic?

Why did I start to think that addiction and abdnction were related? Because the veterans were telling me that they were addicted to certain things—like caffeine, sweets, pasta, or popcorn—and, at the same time, they were avoiding other exposures such as filling their cars with gasoline, diesel exhaust, or alcoholic beverages and foods they used to enjoy, like pizza and chocolate. The fact that these polar behaviors were occurring in the *same* individual caught my attention. There are a number of ways in which abdnction resembles addiction. When chemically intolerant individuals first recognize and begin to avoid substances that trigger their symptoms, they experience withdrawal symptoms that mirror those of a drug addict. Commonly, these include headaches, fatigue, irritability, depression, myalgias, and cognitive difficulties, as well as gastrointestinal problems and sensitivity to physical stimuli like bright light and noise, resembling alcohol withdrawal—a hang-over. Following withdrawal, both drug addicts and the chemically intolerant reach a clean baseline. At that point, they tend to avoid known triggers. But reexposure may initiate cravings. Some chemically intolerant individuals say that certain exposures, like diesel exhaust, can set off cravings for chocolate or other foods.

The notion that chemical intolerance and addiction were related crystallized for me when I was invited to submit a paper for the millennial edition of the journal *Addiction*. The entire issue was devoted to theories of addiction. I had never written anything in that field before, and I considered turning down the offer, but writing that paper forced my thinking. It became clearer, at least in my mind, that chemical intolerance and addiction were “flip-sides” of the same coin and that toxicant-induced loss of tolerance might underlie both conditions (*Addiction* 2000;96: 115-139).

EXPLORE: How does the chemical exposure change tolerance?

MILLER: That’s the \$64,000 question. It’s still a black box. As with addiction, many different neurochemical pathways appear to be involved. Somehow, these may be altered, and, when that happens, either addiction or chemical intolerance develops. No doubt, the process is complex. Despite decades of research, no one fully understands the neurophysiology of addiction. We shouldn’t expect chemical intolerance to be any simpler. When people become addicted to a drug, a host of neurotransmitters and receptors are affected. At any given moment during the addiction cycle, some genes are turning on, with enzymes or other proteins being produced, while other genes are turning off. And, if you have a plethora of exposures as in a sick building, chances are there will be many more effects. Even cocaine affects multiple pathways. And cocaine is just one molecule. Imagine what hundreds of different VOCs might do.

We need to talk about the close connection between our noses and a part of our brains called the limbic system. One portion of the limbic system, the hippocampus, is vital for memory, concentration, and learning. Another part of the limbic system is the amygdala, popularly known as “emotion central.” The amygdala regulates our mood states and is present only in mammals. The amygdala and the hippocampus are closely connected to the olfactory nerves in the upper part of the nose—only a few synapses away. When stimulated, the olfactory nerves relay signals to the olfactory bulb, which is inside the brain, and then to the limbic system. In fact, the olfactory nerves are the most direct connection between our brains and the external environment. Odors can trigger electrical activity in the hippocampus and amygdala, which is why odors can affect our mood and trigger memories. Some chemicals are able to slip through the membrane of an olfactory nerve, and those molecules—odors are molecules—can migrate retrograde up to the olfactory bulb inside the brain and accumulate there.

We know that, if you expose an animal repeatedly to certain solvents or pesticides, you can actually sensitize the amygdala so that, over time, lesser exposures trigger an electrical discharge. This is called *time-dependent sensitization*. Thereafter, reexposure to miniscule amounts of

the same substance, or structurally unrelated substances, can trigger erratic electrical discharge in the limbic area. If severe enough, seizures can occur. Erratic electrical discharge in the hippocampus disrupts concentration and memory. In 1992, I wrote a paper with Iris Bell, MD, PhD, a psychiatrist at the University of Arizona, about how limbic sensitization might be the basis for chemical intolerance. It was called “An Olfactory Limbic Model of Multiple Chemical Sensitivity Syndrome: Possible Relationships to Kindling and Affective Spectrum Disorders” and was published in the *Journal of the Society of Biological Psychiatry*. This is one of several plausible theories. There are other ideas about how chemical intolerance develops, and they may not be mutually exclusive.

Animal models have helped us understand the role of genes in alcoholism. Studies by Ting-Kai Li, MD, director of the NIAAA, have shown that genetic variations in alcohol dehydrogenase—the enzyme that catalyzes the first step in the metabolism of alcohol—affect alcohol consumption behavior in animals. His research helped confirm the once radical notion that alcohol consumption behavior is genetically influenced. It should not surprise us, then, that differences in people’s responses to chemical exposures—including chemical intolerances—might also be genetically influenced.

David Overstreet, PhD, from the Bowles Center for Alcohol Studies at the University of North Carolina co-chaired the NIH conference. He described rats he has bred for cholinergic sensitivity, which means that they over respond to organophosphate-like chemicals. Remarkably, these animals also have intolerances for structurally unrelated chemicals and foods. Disruption of the cholinergic system doesn’t just affect the brain; it affects the entire body. This is interesting because, once chemical intolerance develops, multiple organ systems are typically involved—the gastrointestinal tract, skin, nervous system, lungs, and so on. Because of this and because some of the most symptomatic patients experienced an initial organophosphate exposure, we think the cholinergic system may play a central role in chemical intolerance and TILT.

Scientists still have much to learn about the cholinergic system. We know perhaps one tenth as much about it as we do about

other neurotransmitters like serotonin or dopamine. There is a reason for this. Pharmaceutical companies, which sponsor new drug development, tend to steer clear of cholinergic drugs because they often produce unwanted side effects. Instead, most research has focused on pathways that offer more precise targets. My fear is that we are learning about the cholinergic system through the back door—as the result of toxic exposures to organophosphate pesticides, chemicals that did not exist before World War II.

EXPLORE: Why has this been so hard for people to see?

MILLER: Number one is the fact that different people have different symptoms after the same exposure. So it is hard for the patients and their doctors to pinpoint the problem.

Another reason this has been hard to see is this phenomenon called *masking*. If you have individuals who are responding adversely to caffeine, they may be able to figure it out. But, if they are also reacting to foods in their diet and various chemicals in the air, then the stimulatory and withdrawal effects of all of these exposures overlap and the individual just feels bad most of the time. People's ability to tell you which exposures are causing which symptoms depends on how masked they are and how often they are exposed to chemicals and food triggers. The ideal would be to unmask them.

What we need are environmentally controlled hospital rooms where patients can breathe clean air and eat organic foods for a few weeks. They may need to fast, or at least avoid common foods that may be causing their problems. Typically, patients will go through a withdrawal period during which they report feeling terrible, as if they were going through withdrawal from a drug. After a few days in the clean environment, they reach a clean baseline. At this point, we say they are unmasked. They may report restful sleep and feeling better than they have in years. Next, we can reintroduce foods and other suspected exposures one at a time. We usually start by testing single foods, so we can identify a safe diet. If they respond adversely to any item, we eliminate that food. Next, environmental exposures are reintroduced, at very low levels. Unmasking patients beforehand allows us to determine more re-

liably which exposures are triggering their symptoms.

The value of an environmental medical unit is that it allows us to eliminate most chemical and food triggers simultaneously so that test exposures can then be administered in the absence of background symptom noise. A unit built for research purposes would provide simultaneous diagnostic and therapeutic benefits for patients. It would also enable scientists to observe how our genes respond to various exposures, information that would greatly advance our understanding of gene-environment interactions.

The ideal research study would be to take a cohort of 30 people who share the same diagnosis, such as lupus or severe asthma or autism, and put them through this intervention. Then we could see whether most or all of their symptoms clear up. Ninety percent? Sixty percent? How many recover fully? Studies of this kind are necessary if we are to understand how environmental exposures contribute to chronic illness.

A few years ago, we took a delegation of researchers from this country over to Japan to see the environmentally controlled hospital units there. You see, they read our book and flew over to interview us. Then they went home and built an environmentally controlled hospital unit. And they did it extremely well. They put their best medical and engineering minds to work on the project. The research unit we visited in Tokyo, which is a showcase facility, is located in the Kitasato University Hospital. Like the United States, Japan has experienced problems with sick schools and sick buildings, and its citizens asked the government to intervene. So the Japanese government funded four environmentally controlled hospital units.

Healthcare costs for the chronic conditions we have been discussing are enormous and their social and personal costs staggering. Many conditions—for example, autism, allergies, autoimmune diseases, asthma, ADHD, and chronic fatigue—appear to have increased in prevalence over the past few decades, and everyone is sitting around wondering why. But, when I consider the fact that we spend 90% of our day indoors, the drastic reduction in fresh air entering

our buildings and homes since the mid-1970s, and the tens of thousands of synthetic organic chemicals that have been introduced since World War II, then, for me, there is no mystery.

My dream is that one day there will be environmentally controlled hospital units available to patients at most large hospitals, just as we have cardiac care units and intensive care units today. At the same time, it makes no sense to admit patients to a hospital and help them get better if afterward they go home and are reexposed. So there is a whole education process that has to go with this. I find that people who were never terribly concerned about the environment suddenly become personally invested when they realize that their own illness or their child's illness may be the result of chemical exposures.

EXPLORE: This has been very informative. Is there any other point you'd like to make before we close?

MILLER: Yes. I'd like to talk about how theories of disease develop. As we said earlier, all science begins with observation. Back in the late 1800s, doctors observed that certain illnesses spread from sick, feverish individuals to others nearby. They hypothesized that there must be some sort of "germ" that travels from one person to another. And that was how the germ theory of disease began. It was very crude. To use the word "germ" today is almost laughable. We now have specific names for all of the microorganisms that researchers have identified.

In the late 1800s, we were only at the early observational stage in terms of our understanding of infectious disease. A London physician, Dr. John Snow, first noticed that contaminated water spreads cholera. Thirty years went by before Koch discovered the bacterium that causes cholera. So scientific evidence to support the germ theory took decades to gather. What is the hallmark symptom of an infectious disease? Fever. Fevers helped doctors recognize they were dealing with a special class of diseases.

So, now, let's look at the 1900s, when people began to recognize allergies. A bee sting might be uneventful. But, if a person were stung a second time and went into shock, people might reason that something must have altered that person's sen-



Shown here in her office in San Antonio looking at dust mites under the microscope, Dr. Miller is interested in the role of low-level chemical exposures in a wide variety of illnesses.

sitivity. Some “anti-gen,” formed as a result of the initial encounter, must have caused the person’s body to produce “antibodies,” which hung around and led to anaphylaxis with the second sting. Again, this was a very crude explanation, but sci-

entists were doing their best to describe a new set of observations. These observations were the forerunner of the immune theory of disease. Decades later, IgE—the antigen involved in allergic reactions—was discovered. Many different kinds of anti-

gens cause allergies—drugs, microorganisms, pollens, foods, and others—so it was a complex phenomenon, but, eventually, we sorted it out.

Today, the medical profession finds itself baffled by yet another new group of illnesses, one that is characterized by multi-system symptoms and new-onset intolerances. Once again, we may be in the early observational stage of a new general disease mechanism, or theory of disease. The appearance of multisystem symptoms and new-onset intolerances following well-characterized exposures in more than a dozen countries is a compelling anomaly. Instead of germs or antigens, certain synthetic organic chemicals are being implicated as causal agents. Just as fever was the hallmark symptom that led us to the germ theory of disease, these patients’ multiple food, drug, and chemical intolerances are hallmark symptoms for the TILT theory of disease. And, just as microscopes allowed us to see germs for the first time, environmentally controlled hospital units are necessary for us to be able to “see” the underlying dynamic in chemical intolerance. This new tool would enable us to determine scientifically whether a person’s asthma or autism or autoimmune disorder is the result of environmental exposures.

Sadly, while the Japanese government has provided funding for four environmentally controlled hospital units, no research unit currently exists in the United States, despite the fact that several federal and professional workshops have endorsed this approach as their top priority.

People always ask me why our government hasn’t supported research using an environmental medical unit. In fact, Congress has requested funding on three separate occasions, but, each time, the funds have been diverted. Meanwhile, more Americans are coping with chronic illness, and our healthcare costs continue to rise. We are not addressing underlying causes. Personally, I cannot think of a better investment.

For a free copy of the Environmental Exposure and Sensitivity Inventory (EESI), please e-mail Dr. Miller at millercs@uthscsa.edu.