

Once a contested illness, chemical sensitivity has been validated by research revealing the biological glitches driving victims to extremes.

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Allergic to Life

One night in August 2005, Scott Killingsworth, a 35-year-old software designer in Atlanta, dragged his dining-room table out to the porch and lay down on it. The house he'd just rented — on 2 acres in an upscale suburb north of the city — was meant to be relatively free of man-made chemicals, his refuge from the world. For years he had been experiencing debilitating reactions to a cornucopia of common chemicals that others don't even notice.

But this house, like the one before it, was making him sick with flu-like symptoms — nausea, headaches and muscle stiffness.

Lying on the table and breathing in fresh air, Killingsworth thought back to the morning seven years ago when his office was sprayed with Dursban, a potent organophosphate pesticide that has been banned for indoor use since 2000. Within minutes of the pesticide treatment, he was unable to concentrate, and he felt like he had a bad flu. When he returned to the office a week later, he felt sick again. He asked his supervisor to move him to a different office.

"I thought that was the end of it," he recalls. "But that was the beginning of it."

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Instead of recovering, he got sicker as each year passed. Newly renovated buildings, fresh paint, gasoline odors, pesticides, herbicides — the list of substances he reacted to grew longer and longer. After his apartment was painted by mistake one day while he was at work, he got so ill that he took a leave of absence and moved. But each subsequent home left him with the familiar panoply of headaches, flulike symptoms, insomnia, the inability to concentrate and fatigue. After sleeping on his dining table for a week, he bought a camping cot and slept on it each night for years. When he became reactive to the almost imperceptible outgassing of chemicals from his own computer, he switched to a Bluetooth keyboard and looked at his computer monitor through the porch window.



Scott Killingsworth reads a letter inside his renovated travel trailer.

Before he got ill, Killingsworth had a girlfriend and an active social life. As his unusual illness escalated, he began to live like a hermit. During his final two years in Georgia, he had fewer than 10 visitors, he says.

Finally, in fall 2007, nine years after his run-in with Dursban, Killingsworth applied for Social Security disability, packed his belongings, and drove west in his Honda Civic to search for housing among a community of folks like himself — all suffering from what is loosely called "environmental illness" — in the remote high desert of Arizona. Today, in his 40s, he lives in a renovated travel trailer specially designed for his sensitivities: It has porcelain tile floors, sealed walls and sealed wood cabinetry. He camps alone and with friends. He relies on solar power, hauls his own water at times and moves seasonally to avoid extremes of heat and cold. Most days, however, he can tolerate the trailer only for a while, even with windows open, and sleeps on a cot in the back of his truck, under the protective camper shell.

A TWO-STEP PROCESS

If anybody can understand what happened to Killingsworth, it is physician Claudia Miller, an environmental health expert at the University of Texas School of Medicine in San Antonio, who studies a phenomenon she calls toxicant-induced loss of tolerance (TILT). The word *toxicant* refers to a man-made poison, such as Dursban, whereas a toxin is a naturally occurring poison produced by living cells or organisms, such as spider venom.

TILT, says Miller, is a two-step process: First, a susceptible individual gets sick after toxic exposure or exposures. But then, instead of recovering, the neurological and immune systems remain damaged, and the individual fails to get well. The sufferer begins to lose tolerance to a wide range of chemicals common in everyday life. The latest research, both in the United States and abroad, suggests that brain processing itself is altered so that the neurological setpoint for sensitivity falls. The person, now sick, becomes highly sensitive to chemical exposures. The individual is like a fireplace after the original fire has died down: The embers still glow a brilliant orange, ready to burst into flame with the slightest assistance.

Individuals with TILT can become increasingly more reactive over time, until they find themselves responding adversely to the mere whiff or dollop of everyday chemicals — at concentrations far below established toxicity. The triggering substances are often structurally unrelated and range from airborne molecules to ordinary drugs and supplements, lotions, detergents, soaps, newsprint and once-cherished foods like chocolate, pizza or beer. Exposures result in a bewildering variety of symptoms such as cardiac and neurological abnormalities, headaches, bladder disturbances, asthma, depression, anxiety, gut problems, impaired cognitive ability and sleep disorders.

Because so many substances seem to spike these overlapping reactions, and because not everybody is universally reactive to exactly the same substances, it's hard to ferret out cause and effect. And that has, until recently, left these individuals consulting many different specialists, presenting a picture that looks deeply neurotic.

When chemically intolerant patients first came to the attention of the medical profession in the 1980s, their condition was called "multiple chemical sensitivity" (MCS), and there was enough curiosity to spark studies. But those studies never turned up anything definitive, and nobody thought to look at the actual processing going on in the brain. They would test patients by exposing them to odors in a "blinded" situation, where they did not know what they were being exposed to, or they were told harmful odors were present when there were no odors at all. The patients often failed to demonstrate any consistent response. Studies on detoxification pathways — the immune mechanisms by which the body dismantles toxins — were few and far between; research never explained how certain exposures could snowball into the profound dysfunction reported by this hobbled patient group. Immunological

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To escape from the chemicals that sicken him, Killingsworth made the remote high desert of Arizona his new home.

JOSHUA LOTT

abnormalities were investigated, but not one was ever consistently tied to the condition overall.

So for decades, these patients were cast aside as mentally ill. If you see a person wearing a honeycomb mask in the detergent aisle of the supermarket, if they tell you that the fabric softener scent you love is making them ill, if they say your perfume is causing headaches and asthma and that the carpet store causes brain fog, irritability and depression, your reflexive response may just be, "You may be sick, but you are probably sick in the head."

SCIENCE FOR TOXIC TIMES

For scientists studying the illness, however, that view has changed, in large part due to Miller's indefatigable research and her groundbreaking finds. According to a July 2012 study of 400 primary care patients (published by Miller and her colleagues in the popular family practice journal *Annals of Family Medicine*), 22 percent of individuals with chronic health issues suffer from some degree of chemical intolerance. That's more than one in five — and, says Miller, they are vulnerable to TILT if life happens to toss them too much toxic exposure. "The fact that chemical intolerance is so prevalent, yet unrecognized, is important for primary care physicians," says physician David Katerndahl, Miller's colleague and lead author on the study. "On the one hand, simple therapeutic approaches (avoiding chemicals) may be quite effective, while on the other hand, conventional treatments (allergy shots, immune suppressants) may fail. This means that we must change our clinical paradigm with these patients."

The new study is based on an inventory of 50 questions called the QEESI (the Quick Environmental Exposure and Sensitivity Inventory, available for free at familymed.uthscsa.edu/qeesi.pdf). The QEESI isolates sensitivities to common triggers, such as diesel, paint thinner, foods and products like fabric softener. It is very effective at culling the one in five individuals who are vulnerable to severe TILT, and it has been validated in Sweden, Denmark, Japan and the United States.

It is severe TILT, where the individual's life is seriously impacted, that worries Miller, however. "In the study, I was astounded to find that over 6 percent of people visiting a primary care clinic for any kind of chronic health condition were greatly affected by TILT, based on their symptoms and chemical and other intolerance scores from the QEESI. By greatly affected, I mean that they had chronic health symptoms that were severe, and they scored high on sensitivities to common chemicals, foods and medications," says Miller. "Another 15.8 percent were moderately affected, with scores that were still well above average." Miller's mission is to catch those vulnerable folks, like fish in a net, before they run headlong into a toxic exposure that derails their lives. She would like to see the QEESI given as standard practice along with the typical sheaf of forms patients fill out.

"TILT describes a genuinely new class of diseases unique to our toxic, modern times," says Miller. "People suddenly cannot tolerate chemicals and exposures they'd tolerated their whole lives. It's the hallmark of TILT. Some people I've counseled even use it as a verb. They say they've been 'tilted.'"

NAVIGATING A TILTED WORLD

The two-step process of TILT — getting sick upon toxicant exposure and failing to get well — may be driven by epigenetic changes, which occur when the environment alters the expression of genes without changing the core DNA code itself. "Environmental events can dramatically impact gene activity," explains reproductive endocrinologist Frederick vom Saal of the University of Missouri-Columbia. Vom Saal has spent several decades researching the potent effects of everyday low-dose exposure to chemicals like bisphenol A (BPA) that are known as endocrine disrupters. These chemicals act like hormones and have profound influences on health, particularly during fetal development. It turns out that surprisingly low doses can be potent regulators of gene

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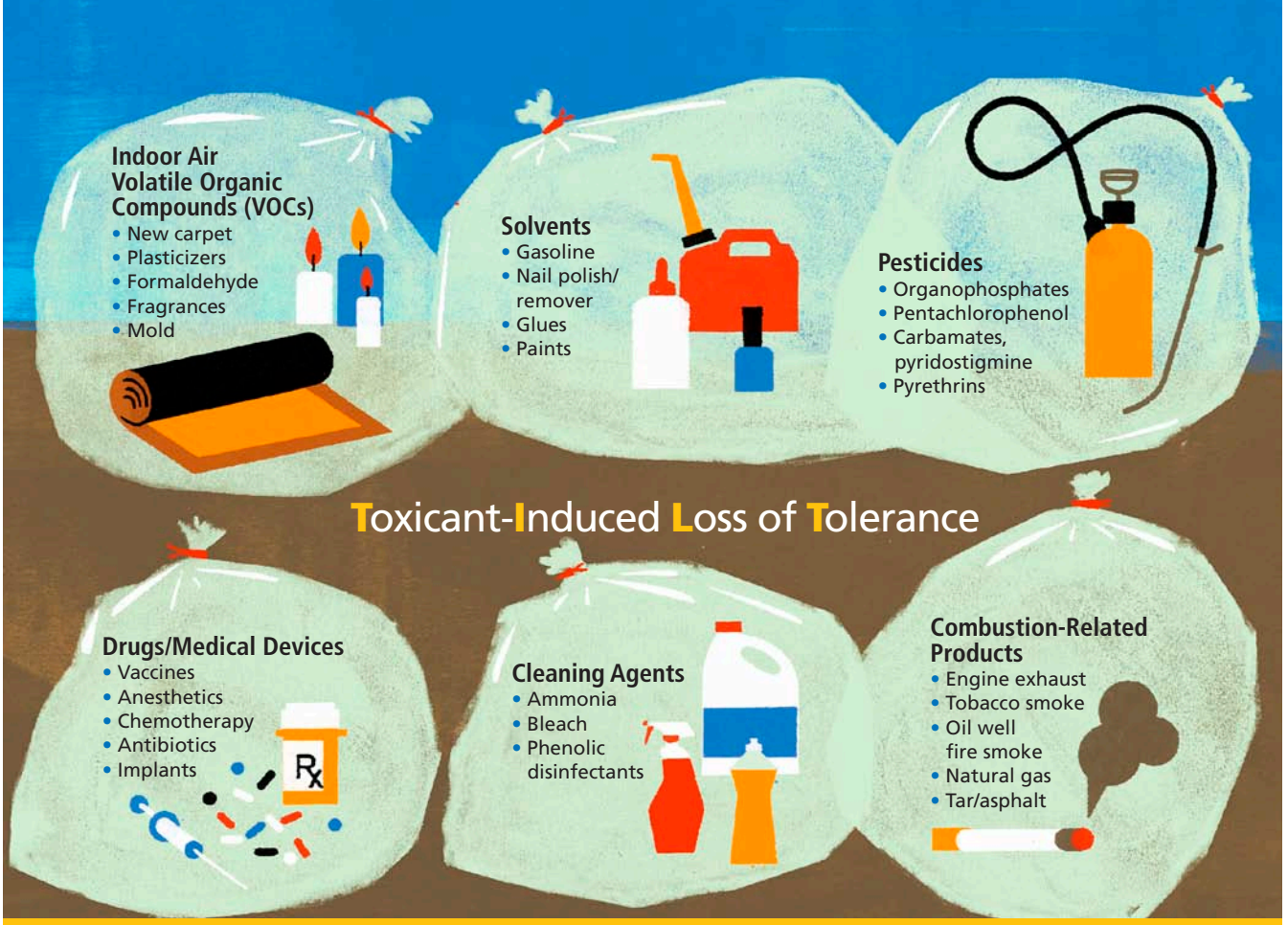

After exposure to certain chemicals, some people may be unable to tolerate ordinary cleaning fluids, perfumes or other substances shown here.

activity, while high doses simply shut activity down. "Once genes are switched on," says vom Saal, "and once you are sensitized, you essentially have a reprogrammed cell. And it's hard for that cell to go back to its original state. You will find, for instance, that mammary tissue is more vulnerable to cancer later in life, or puberty occurs earlier than normal because of low-dose exposures in the womb. Although I personally study epigenetics during development, evidence suggests these kind of events occur throughout life."

In the world of TILT, dose does not make the poison. Dose plus host makes the poison — and host susceptibility is the missing link. In the genetically vulnerable, too much toxic exposure seems to recalibrate the body for life. "All changed, changed utterly," as poet William Yeats might say; a new person emerges, for whom the ordinary world is now littered with seemingly toxic land mines, often not perceived until stumbled upon, and yet the sufferer looks on as others blithely dance over those same land mines without the hint of a problem.

To Miller, the kind of pesticide poisoning Killingsworth suffered is a truly elegant, if terrifying, example of TILT. In the mid-1990s, she and her colleague Howard Mitzel surveyed 37 individuals who had become permanently ill after an exposure to organophosphate pesticides, and another 75 individuals who got ill after extensive remodeling in the home or office. In both cases, exposure to toxic substances left a permanent damaging footprint, though pesticide sufferers were by far the sicker group. At the time of their pesticide exposure, 26 of the 37 pesticide individuals were working full time. By the time of the survey (an average of about eight years after exposure), only two of the pesticide individuals were able to work full time. They reported that their illness had affected every aspect of their lives.

TILT looks much the same across cultures and countries. Miller co-authored a textbook, *Chemical Exposures: Low Levels and High Stakes*, with MIT policy and technology professor emeritus Nicholas Ashford. In that book, Ashford reported on his research in nine different European countries, and he found the same patterns of inexplicable new-onset intolerance to chemicals. "I simply asked physicians if they'd ever had patients who developed unusual and inexplicable responses to anything that had never bothered them before," he says, "and I inevitably got a nod yes, and stories." Miller, meanwhile, has documented similar reports from the United States, Canada, Japan, New Zealand, Great Britain and Australia.

New-onset intolerances and multisystem symptoms have shown up in sheep dippers in rural areas of Europe (sheep dip is an organophosphate pesticide), homeowners in Germany exposed to a toxic wood preservative, individuals breathing fumes from massive oil spills, radiology workers in New Zealand who inhaled chemicals while developing films, and individuals living or working in newly remodeled buildings. In 1987, 225 workers renovating the EPA's headquarters in Washington, D.C., got sick after extensive remodeling of a poorly ventilated office building that included the installation of 27,000 feet of new carpet. Although most recovered, 19 developed TILT and became so disabled over the long

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term that they sued the building owners.

Gulf War veterans were another "tilted" group. Their illness was long the subject of controversy, and even dismissed as a form of post-traumatic stress disorder, but it has recently been accepted as genuine. Miller found that a surprising number of Gulf War veterans turned out to suffer from TILT. "Of 700,000 who went to war in 1990, 250,000 came back with chronic illness," she says. "A CDC study found that sick Gulf War veterans reported more chemical intolerances than their healthy counterparts. They had multiple toxic exposures, including pesticides in their tents, smoke from oil fires, anti-nerve-gas pills and diesel fuel poured on the ground to keep the sand down."

When Miller visited veterans, some had signs on their room doors: "Don't enter if you're wearing fragrance." Many were having trouble tolerating medications. One veteran had sent his wife a favorite perfume from overseas, but when she wore it on their car ride home, he became so sick he asked her never to wear it again. They'd report they felt better on a vacation in, say, the high mesas of Colorado, and spaced out and sick driving in heavy traffic.

They FELT BETTER on vacation in the high mesas of Colorado and SPACED OUT and SICK driving in heavy traffic.



Claudia Miller is an environmental health expert at the University of Texas at San Antonio.

A RADICAL PATH

Miller did not start her career thinking about low-dose poisons. She was a newly minted industrial hygienist with long, blond hair and wide-set blue eyes when, in 1979, she was hired for the United Steelworkers union in Pittsburgh. The union had 1.2 million mostly male members. "I loved visiting steel mills, smelters and mines," she recalls. "I found it fascinating to go to coke ovens and see steel being made in the blast furnace and watch parts made by pouring molten metal into molds in foundries."

Miller sometimes got headaches after a few hours in the same environments the workers had worked in for decades, but she didn't think much about those headaches at the time. She was just trying to make sure the companies complied with standards set by the Occupational Safety and Health Association (OSHA). But then the National Institute for Occupational Safety and Health (NIOSH) asked her to examine some female steelworkers diagnosed with psychological and management problems. The women soldered piecework for electronics in two different plants. They worked in rooms without fume vents, and they complained of headaches, fatigue and difficulty concentrating. In a paper she presented that year at a NIOSH symposium, Miller proposed that toxicants in fumes from the soldering might be responsible for their complaints. "I was the only non-psychiatrist at the meeting," she recalls, "and by the time I finished my talk, the experts were lined up at the microphone to attack my ideas."

It was another heretic, controversial Chicago allergist Theron Randolph, who first lent support. Randolph broke with his profession around 1950 and had begun to test and treat individuals for a wide range of sensitivities vastly different from typical allergies, which could be diagnosed through the appearance of elevated immune cells, called immunoglobulins, in the blood. Randolph was convinced that his patients suffered from food and chemical sensitivities that couldn't be measured in traditional ways. He invited Miller to attend his weekly staff meetings, where cases were discussed.

When Randolph took a patient history, Miller recalls, it lasted hours. He would begin an appointment by saying, "Tell me the last time you felt truly well, and go from there." He would type out the history directly as the patient talked. Miller remembers details like, "She felt ill in the train station in Chicago. … She felt nauseous on the foam rubber mattress."

Randolph would "hospitalize" patients for a few weeks in specially constructed units near his Chicago offices. During their confinement, they breathed filtered air, slept on untreated cotton bedding, drank purified water and fasted for days. Their symptoms, from arthritis to headaches to fatigue, would often melt away. Then he would do blinded challenges on patients — feed a patient an organic apple and a sprayed apple, or expose them to a whiff of copy paper in a glass jar. Symptoms such as migraines or joint pain would recur in response to whatever substances the individual patient was sensitive to. Avoiding those triggers was the inevitable prescription when they left the clinic.

"Many patients were able to get off their medications and get well. These people were reacting to tiny doses of substances, doses that simply should not be causing symptoms. It broke every paradigm of medicine I knew," explains Miller. "I decided to go to medical school, and then to work as a researcher within a university setting, to establish scientific credibility for this amazing work, which at the time, virtually nobody in academic medicine or science believed."

BODY OF EVIDENCE

Two decades and hundreds of peer-review papers later, Miller has amassed a fascinating body of research that suggests a model by which a genetically vulnerable person might succumb to TILT. One major insight draws on the fields of epilepsy and chronic pain syndrome, both of which are associated with abnormal brain activity. In some cases of chronic pain, what begins as an acute, localized injury spreads and becomes a generalized pain syndrome known as reflex sympathetic dystrophy. Pain signals seem to flame across the entire

OPPOSITE: KEITH NEGLEY. THIS PAGE: MARK C. GREENBERG

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Jerry Gelineau and Claudia Miller, researchers at the University of Texas at San Antonio, measure a patient's blood flow to the brain to find evidence of TILT.

body, and the condition is debilitating and difficult to treat.

Similarly, abnormal brain activity and processing is well known in the field of seizure disorders; temporal lobe epilepsy has been traced to a phenomenon called limbic kindling, in which repeated, intermittent, low-intensity stimulation across the limbic structures of the brain may eventually lead to a seizure.

In fact, Miller hypothesized that a process similar to kindling may be driving the pain and sensitivities documented in TILT. Toxicants like solvents, pesticides or volatile molecules from oil spills can travel straight into the brain via the olfactory receptors — nasal neurons that number in the many millions, thickly studding the inner lining of the nose. Our brains are exquisitely primed to respond to nasal receptors. Not surprisingly, even healthy individuals show significant changes in brain wave activity during brief exposures to olfactory stimuli that are actually below the sensory threshold and not even consciously perceived.

"The lack of a blood-brain barrier in the olfactory system allows chemicals direct access to the limbic system," says Miller. "And the olfactory pathways are already known to be particularly susceptible to electrical and chemical kindling. Moreover, most chemical exposures are intermittent, which is the kind of exposure known to potentiate kindling and sensitization." Intermittent lower-dose exposures can be as toxic as a single higher-dose exposure; Miller cites monkey research showing that either 10 nontoxic weekly doses or one toxic dose of an organophosphate pesticide led to the same increase in brain wave activity as measured by electroencephalogram, or EEG.

Miller hypothesizes that exposure to toxicants permanently decreases the threshold needed to excite the limbic network, setting the stage for a phenomenon much like kindling. "It's not actual kindling in the strict scientific sense of inducing a seizure," she notes, but that sensitization could theoretically lead to permanent changes in function — and permanently increased reactivity to chemicals processed through the olfactory neurons.

Supporting her view is research from the Danish Research Centre for Chemical Sensitivities at Copenhagen University Hospital Gentofte, where scientists have demonstrated that individuals with chemical intolerance show greater sensitization in the central nervous system. The center's research has found that 27 percent of the Danish population has some noticeable sensitivity to chemicals. A much smaller number, 0.5 percent, is so sensitive that lifestyle must dramatically change.

In another study, researchers at the center chose 15 chemically intolerant patients from those who had come to the center asking for help. They also looked at 15 healthy individuals. Then they injected capsaicin, the active molecule in hot pepper, under the skin and lightly tapped the area with a blunt, rigid nylon filament — starting at six centimeters away, and tapping closer and closer to the injection site. When the pricking sensation changed to pain, it was recorded.

Not only is capsaicin odorless, it is known to induce a pain response modulated specifically by the central nervous system. "It was really interesting," comments dermatologist Jesper Elberling, the lead author on the study. "In chemically intolerant individuals, the area of skin pain was significantly greater, as were the reported levels of pain. Something is going on in the central nervous system — some process of sensitization and heightened response."

The center is now planning a study to look at genes involved in sensitization in the brain, to see if they are activated in chemically sensitive individuals. "In 2010, we unsuccessfully tried testing genes involved in detoxification and concluded that variants in detoxification genes and pathways are less important than previously thought," says the center's director, Sine Skovbjerg Jakobsen. "We don't find consistent immunological abnormalities, nor do we find an abnormal sense of smell." So something else is going on in the brain. Much like Miller, the Danish researchers suspect that sensitization of the brain, probably by some kind of kindling process, could be at the root.

Astoundingly, in 2010, Elberling reported on a single case study where electroshock therapy (ECT) actually put severe chemical intolerances in remission. ECT has been proven effective in severe depression and refractory pain syndromes — its impact is in the brain itself, where it seems to reset thresholds of reactivity. The 45-year-old male patient had become so chemically intolerant that he had been on sick leave for two years, had moved out of his home and could only see his children outside, not indoors. He was so isolated, he felt "a desperation he feared would lead to severe psychological breakdown," says Elberling.

Before his illness, the patient worked as a stock manager in an industrial spray paint company. "At pre-ECT baseline," says Elberling, "his self-rated chemical sensitivity symptom severity was 95 out of 100. After the third ECT treatment, he

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declined to 30 out of 100, and he gradually resumed ordinary life activities." He was able to entertain, shop and spend time with family and friends. He was put on standard maintenance therapy (an ECT treatment every two weeks) for four months with only mild residual sensitivities. "It is likely that ECT triggered the recovery process of brain regions reorganized in this chemically intolerant patient," Elberling says. Although this example is extreme, it does point to a brain-driven mechanism that could inform future research.

Chemically intolerant individuals also show dysfunction in brain imaging on a SPECT scan, which tracks blood flow through tissue. That work was done at the University of Hebron in Barcelona, where researchers followed 10 chemically intolerant patients over a two-year period. Patients' symptoms were chronic and reliably triggered by exposure levels that previously did not bother them. To do their study, the Hebron scientists evaluated intolerant patients by SPECT scan. Then, a week later, each of those patients entered a chamber with a healthy individual. For varying periods of time, both were exposed to ordinary fumes from paint, perfume, gasoline and an aldehyde substance of the sort often used to manufacture perfumes or drugs. After exposure, there was a significantly greater decrease in blood flow in specific brain areas, particularly those involved in odor processing, in the chemically intolerant patients.

> In a GENETICALLY VULNERABLE individual, too much toxic exposure seems to RECALIBRATE the body for life.

Miller, meanwhile, has found decreased blood flow through the central artery in the brains of Gulf War veterans suffering from TILT. Eight male veterans complaining of Gulf War illness and eight healthy veterans participated in her study. The veterans were stationed in front of a computer and given routine short-term memory tasks while being exposed to clean, filtered air or air with imperceptible amounts of acetone. Miller and the team told the subjects the air contained acetone whether it did or not. The content of the air had no impact on healthy subjects, but for sick Gulf War veterans, it was a different story. When the air contained trace amounts of acetone, the blood flow through their large middle cerebral artery was significantly slowed.

"I didn't think TILT was real until we completed this study," says physiologist Leonid Bunegin, a colleague of Miller's at the University of Texas, who helped design and carry out the research. "It was the first hard-core study to show a definitive correlation between brain function and low-level chemical exposure."

CONTROVERSY REIGNS

Of course, skeptics remain. Not everybody is convinced the new model is valid. As recently as 2008, an Italian case study by University of Padova psychologist Gesualdo Zucco concluded that a chemically intolerant individual had "a debilitating psychological disorder in need of treatment." After a car accident in 1992, the 36-year-old patient complained of chemical sensitivities so severe she sometimes vomited or fainted. In a laboratory setting, she was exposed to a "blank stimulus" (no odor at all), odors she'd earlier rated as pleasant (coconut, banana) and odors she said caused symptoms (turpentine, paint). Symptoms she reported were directly related to the information she was given about the safety of the odors. If she was told that a blank stimulus or a pleasant odor was actually harmful, she reacted badly; if she was told it was an odor she'd rated as pleasant, she did not react badly. "There was remarkable consistency across trials," says Zucco, "and it is noteworthy that at first the patient truly believed her disease was biological in origin." This is an attitude very common among TILT patients, since they label themselves as afflicted by a physical disease.

After the study, the patient accepted Zucco's conclusion that the symptoms were psychological. Cognitive psychotherapy, he says "allowed her to manage most of her symptoms, and for several years she sent me Christmas cards letting me know she remained improved."

But even Zucco doesn't insist that all cases are psychological. Some may "have a biological or organic origin," he says. "The point of this study was that it was able to distinguish the difference."

Miller has a different point of view. TILT, she says, emerges from a more sensitive, highly excitable limbic system. Asthma, depression and panic disorder run in families of sufferers. Shyness, which can be an avoidance behavior to control stimuli, is more prevalent, too.

In other words, she says, personality constructs emerging from the basic biology of the brain can be yet another marker that the individual is at risk for TILT, and easier to sensitize to the disease.

Someday, Miller hopes, you will walk into a physician's office for a consultation, and along with the typical sheaf of papers about your health history, you'll be given a different set of questions: the QEESI. You'll checkmark, on a scale of one to 10, if you feel sick after breathing diesel exhaust or paint thinner, have unusual food cravings, use a gas stove or fabric softener at home, seem oddly sensitive to medications, or suffer inexplicable complaints such as dizziness, rashes, difficulty concentrating, headaches and mood swings. You will be given your QEESI score. And if you're one in every five who appears to be at risk for TILT, you will be counseled on lifestyle and dietary changes.

You will be like the psychologist that Miller spoke to after presenting findings at a conference.

"The woman took the QEESI, and found she was at greater risk for TILT. She had just ordered new, synthetic carpet for her entire house, and she said to me, 'I'm not sick, and I don't want to get sick. I'm canceling the carpet order and installing ceramic tile instead.'" D

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