

MCS: A Sensitive Issue

Dianne Wiganowsky heard an unusual noise outside her house in Cheyenne, Wyoming, in September 1992, so she went to look out her screen door. She did not expect the potent stream of lawn chemicals that struck her in the face, nor could she know that, at that moment, her health would begin to decline to the point that most of her time is spent monitoring pain.

What hit Wiganowsky was a strong mix of active agricultural organophosphates and fungicides that a lawn care company was spraying, carelessly, with a bullet nozzle on a neighbor's shrubs and trees. The powerful stream hit Wiganowsky at the door with such velocity that the chemical mixture ran down the rear wall of her living room.

Two days later she had "the worst flu in the world," followed by lethargy so severe she couldn't get out of bed, succeeded by pneumonia. She visited five different doctors, all of whom couldn't find anything wrong, and all of whom referred her to a psychiatrist. When Wiganowsky, 54, went outside, her eyes turned red and bloodshot, her lips cracked and bled, and pain roamed her body, settling in different areas.

Eventually, Wiganowsky got sick after bathing because of chlorine in her water, and she stopped using her favorite shampoo when it burned her scalp. She can't stand the prickly pain she experiences after using deodorant or lipstick, and a whiff of perfume makes her nauseated and sick. After sitting on the carpet in a friend's new home, Wiganowsky got blisters on her thighs. She is now engaged in an unhappy struggle to avoid nearly everything.

Until recently, most physicians, like the ones Wiganowsky first saw, would refer such patients to a psychiatrist. Many still do. But a segment of the medical profession is giving more and more credence to evidence suggesting that Wiganowsky and others are victims of an illness that has been variously dubbed environmental illness, total allergy syndrome, chemical AIDS, and, most commonly, multiple chemical sensitivity (MCS). Some patients and physicians call MCS "20th-century illness" because they believe it is caused by a growing environmental load of chemicals in the modern world. To someone who has become sensitized to these chemicals, sniffs of such common products as hair spray and laundry soap produce myriad symptoms, including headaches, rashes, depression, confusion, and fatigue.

After talking with all the experts she could find, including the Centers for Disease Control, Wiganowsky now knows

that MCS is not recognized by many physicians. So, to control her constant pain, Wiganowsky throws away anything that causes her pain. But what bothers her most, she says, is that many people with symptoms like hers are dismissed by some as wackos. "There can't be so many people that are crazy in a similar way. All I ask for is a benefit of the doubt," she said. That may be as much as the scientific community is willing to give. MCS is perhaps medicine's most controversial disorder—if it can even be called a disorder.

Recognition of a Problem

The malady is one that baffles medical experts. They disagree whether MCS is real, and they argue over its definition, etiology, and treatment. Detractors point out that most who suffer from MCS have a lifelong history of medical problems which usually includes depression, and they wonder why it seems to strike mostly white, middle-aged, middle-class women. Most academic allergists and immunologists reject an MCS diagnosis as unconventional and unproven, pointing to little evidence of immune system dysfunction. Patients who can't find solace in the hands of establishment medicine turn to a breed of medical practitioners called "clinical ecologists" who believe that single or multiple exposures to a wide range of chemicals, even foods, can cause hypersensitivity. More than 20 patient-support newsletters are published annually, and some of the terms they use to describe themselves are "universal reactors," "chemics," and "canaries." Other patients, wary of the controversy, tell their friends they suffer from a more politically correct disorder, chronic fatigue syndrome, which some people believe overlaps with MCS.

The scientific debate centers around this question: is MCS a real clinical condition, a form of psychiatric illness, or, as has been recently proposed, a combination of both? There is a growing number of clinical observations concerning patients who report multiple chemical sensitivities and investigators who might propose a mechanism or model to explain this syndrome, but few of these observations or models have been rigorously tested.

Although believers and skeptics are still far apart, the issue of the health consequences of exposure to an onslaught of chemicals has been further advanced in the public, to the point of some acceptance. Advertisers now tout dishwashing detergent that contains no perfumes or dyes. In June, the U.S. Department of Transportation asked foreign countries not to spray

pesticides on airplanes that land in their countries because passengers were getting sick. The State of California proposed a bill to ban perfume in the workplace. And the popular television show "Northern Exposure" featured a chemically sensitive attorney who lived in a toxic-free geodesic dome in Alaska, isolated from the toxins of industrialization and mainstream society. Many people now accept that some individuals are sensitive to chemicals and that they may suffer varying degrees of illness. In fact, one survey found that up to 30% of the population think they may be somewhat sensitive to chemicals; severe problems are reported by 2% of these people.

Even segments of the federal government seem to be several steps ahead of the scientific community in their willingness to accept chemical sensitivity. In 1990, the Americans with Disabilities Act included MCS as a recognized condition, and by mid-1992, the Department of Housing and Urban Development established disability status for the disorder. Congress has even held hearings on whether the chemicals in carpets cause sick-building syndrome, which is thought to be caused by chemicals and inadequate ventilation systems in workplaces. Some people who suffer from sick building syndrome go on to develop MCS.

Organized support groups for MCS victims have sprung up in the last decade, and some have succeeded in pushing research money through Congress. Mary Lamiella, founder and president of the National Center for Environmental Health Strategies, says that she sees new signs of acceptance of MCS everywhere but in the lawsuits that chemical companies are fighting and in the medical and scientific mainstream establishment.

"Things have changed. A lot of industry groups, such as those that make pesticides or perfumes, no longer deny that there is a problem. They are jumping on a bandwagon in a sense, because they fear consequences if they don't respond," says Lamiella.

Arousing Interest

Lamiella admits that the economic stakes are high in whether MCS is ever recognized as a medical condition—insurers, government agencies that provide medical care and compensation, the chemical industry, and others are already being hit with claims and lawsuits, and more would surely follow. But she also claims that "it is only the established medical research community that is comfortable saying that there isn't a problem, and that they don't have any money [for research] anyway."

Indeed, MCS is not recognized by the Centers for Disease Control; it has no

diagnostic criteria or tests, nor is a case definition expected soon. The list of symptoms and chemical culprits changes from patient to patient, but common complaints can include fatigue, concentration or memory difficulties, irritability, nervous tension, depression, daytime drowsiness, food cravings, insomnia, headaches, nasal congestion, muscle and joint aches, ringing in the ears, gastrointestinal distress, and palpitations.

No one knows how many people are sensitive to chemicals. And some physicians who don't believe in MCS call others who do quacks. There is, as Lamiella said, surprisingly little money to research the phenomenon; the few studies undertaken are done using "found" funds—monies borrowed from other research studies.

Government officials say publicly that they are neutral about the issue; some privately add that they are protecting themselves against a political backlash. They also note that numerous symposia convened around MCS, such as the National Research Council's 1991 meeting, have gone nowhere. But despite the skepticism, new views of the interactions between brain and body have caused some regulators and a handful of scientists to take note.

The group taking the lead on MCS is the CDC's sister, the Agency for Toxic Substances and Disease Registry (ATSDR), which is trying to put together an interagency working group to study the issue. Participants will include government agencies such as the National Institute of Occupational Safety and Health, several branches of Health and Human Services, including the National Institutes of Health and the National Institute of Environmental Health Sciences, the EPA, and the Departments of Agriculture, Defense, Veterans Affairs, and Justice.

The working group is an effort to get the dialogue on MCS underway, said Barry Johnson, assistant administrator for ATSDR. "There are serious questions that remain in terms of researching the clinical expression and symptoms of MCS," said Johnson. "But what is not, in my mind at least, in question is that some people are in health distress."

Johnson continued, "This is an issue that the ATSDR has chosen to take seriously, and we want to bring light to a dim subject. But there is no simple path to getting on with scientific and clinical issues. I cannot guarantee that even when we all come together, there will be agreement that there is a need for coordinated activity."

A New Name for an Old Problem?

Chemical sensitivity may not be new. The reclusive, asthmatic French novelist Marcel

Gulf War Veterans

The health problems of thousands of Gulf War veterans may be a mystery to military officials, but Claudia Miller thinks she has a good clue. "Many of these veterans are suffering from the same kind of symptoms seen in people with multiple chemical sensitivity," she said. "We have to look to MCS as a working hypothesis."

An estimated 4000 Persian Gulf veterans returned from the war complaining of widespread health problems such as fatigue, depression, irritability, memory and concentration difficulties, muscle aches, shortness of breath, diarrhea, and a host of other problems which they attribute to exposures in the Gulf. Such exposures include combustion products from oil-well fires, paints, fuels, pesticides, and solvents. Some legislators and veterans have also raised the specter of possible chemical or biological warfare.

Miller became involved in the Gulf War mystery in 1992, when she was hired as a consultant by the Department of Veterans Affairs to examine Gulf War patients and diagnose them. An allergist and immunologist at the Texas Health Science Center at San Antonio, Miller is nationally known for her research on chemical exposure and its relationship to human illness.

In 1993, after Miller was appointed to the VA's scientific panel on Gulf War illness, she pressed for clinical research on MCS in general, because she felt sure MCS was at the root of these veterans' problems. Now the government is going to help Miller test her theory. Earlier this year the Department of Defense and Department of Veterans Affairs came up with more than \$900,000 to supplement \$300,000 that Congress had already approved last year to build an environmental chamber that would allow researchers to test the effects of chemicals, one by one, on MCS patients. It will be the first such federal research project devoted to MCS research.

The environmental medical unit, which several universities are vying for, will have eight beds in four rooms. The unit will be super clean—the air will be filtered, the walls will be porcelain, and furniture will not be made of synthetic materials, which can release a constant low-level stream of chemicals.

After participants "detoxify" in the chamber for several days, they will be given very low levels of a variety of chemicals. Participants will be blinded to these chemical challenges; concentrations will be so low that the subjects will not be able to smell them or taste them. The reaction of the subjects to each substance will be measured and analyzed, and if a subject does react, a battery of physical and neurological tests will follow, such as tests of pulmonary function and cerebral blood flow. Participants will stay in the chamber for about six weeks.

"The environmental unit is critical to ending the debate about whether MCS is real or imagined," said Miller.

Major General Ronald Blanck, commander of Walter Reed Army Medical Center in Bethesda, has gone on record in support of the environmental medical unit tests. Miller's work has great potential importance to determine the etiology of Gulf War disease, Blanck said. "More significantly," he said, "it has tremendous potential benefit to society, which is increasingly being exposed to low levels of a variety of chemicals in the environment."

Proust (1871–1922) spent the last years of his life in a cork-lined bedroom in Paris. He warned visitors not to wear perfume.

A medical syndrome of chemical sensitivity was first described in 1951 by Chicago allergist Theron Randolph, who noted that several of his patients had a "petrochemical problem" in that they became ill when passing through the heavily industrialized areas of northwest Indiana and South Chicago. He advised patients to avoid a wide range of everyday chemical exposures and food to see whether they improved.

His followers, who became known as "clinical ecologists," began to treat self-reporting patients who could find no relief with mainstream medicine. They used a variety of practices, including sauna therapy, vitamin and mineral supplementation, and sublingual

or intradermal administration of chemicals to diagnose and treat the condition.

These practices and diagnoses have resulted in an ongoing acrimonious debate. Allergists have called clinical ecologists "pseudoscientists," convincing many in medicine that the diagnoses and treatment used by clinical ecologists are unproven and ineffective. "I have seen nothing to demonstrate that [MCS] exists," William Waddell, chair of pharmacology and toxicology at the University of Louisville School of Medicine, told the journal *Science*. He blamed the syndrome on an "irrational fear of man-made chemicals." Others go further, accusing clinical ecologists of brainwashing their patients, who did not know what was wrong with them, into believing their illness springs from chemicals.

A stinging rebuke of clinical ecology

was published in a July 1989 position paper in *Annals of Internal Medicine*.

Clinical ecology lacks scientific validation, and the practice of "environmental medicine" cannot be considered harmless. Severe restraints are placed on patients' lives, and in many cases, invalidism is reinforced as patients develop increasingly iatrogenic disability. Treatment by clinical ecologists frequently creates a severe financial burden for patients and imposes significant costs on health insurers and worker's compensation issues.

Fueling this dissent was a spate of reports that suggested clinical significance to the disorder. Specifically, support for MCS sufferers came in 1989 when a study commissioned by the New Jersey Department of Health was issued. The study was conducted by Nicholas Ashford, a chemist and lawyer who is an associate professor of technology and policy at the Massachusetts Institute of Technology, and Claudia Miller, an allergist and immunologist at the University of Texas Health Science Center in San Antonio. Their study concluded that chemical sensitivity is "widespread in nature and is not limited to what some observers would describe as malingering workers, hysterical housewives, and workers experiencing psychogenic illness." Ashford and Miller found evidence of chemical sensitivity in industrial workers, occupants of "tight buildings" with no air flow to the outside, people who live in communities where the water and air are contaminated by toxic chemicals, and other people exposed to chemicals in consumer products, drugs, and pesticides. The researchers said that while no definitive conclusions were possible, "chemical sensitivity does exist as a serious health and environmental problem, and public and private sector action is warranted at both the state and federal levels."

In 1991, Ashford and Miller wrote a book, *Chemical Exposures: Low Levels and High Stakes*, that reviewed MCS literature and proposed biological models of the disorder. Those who considered the syndrome to be due to psychological factors began their own studies. For example, John Selner, an allergist and respiratory specialist at the University of Colorado Health Sciences Center in Denver, claims he can cure most of his MCS patients by systematically deprogramming them to eliminate their "false" beliefs about chemicals. One of the most vocal critics of MCS, Abba Terr, a profes-

sor of medicine at Stanford University, thinks chemophobia is at the root of these patients' illness, although he has said that no form of psychotherapy will help many of them.

After a controlled study, reported in the 15 July 1993 issue of the *Annals of Internal Medicine*, found no physiological differences between MCS patients and controls, except that MCS patients had more depression, Terr wrote an editorial that suggested physicians treat MCS patients with behavior modification therapy. "Seasoned internists, other primary care physicians, and specialists recognize in these patients an all-too-familiar pattern of over-utilization of medical diagnostic facilities because of longstanding unexplained symptoms," he wrote. "The only thing that distinguishes environmental illness or multiple chemical sensitivity from this pattern is the attribution of symptoms to environmental exposures." Other journals weighed in. In 1992, the *Journal of the American Medical Association* published a report from its Council on Scientific Affairs, concluding that MCS "should not be considered a recognized clinical syndrome."

Stories and Studies

At the same time, a handful of researchers pursued physiological mechanisms that could explain MCS. What they have to work with is, in large part, anecdotal evidence that paints a common picture. "Anecdotal stories are just that, but they become very powerful when they come from so many different people across the country," says Lamiella.

Generally, many patients can identify specific circumstances that initiated their illnesses. Some say it began after an overwhelming exposure to chemicals, such as a spill on their job or exposure to pesticides; an informal survey of almost 7000 self-reported chemically sensitive people say their illness started with a pesticide exposure. Or MCS can come on after a new, chronic, medium-level exposure, such as moving into a new house with significant emissions of volatile organic compounds from the building materials or the carpet. After the initial event, symptoms seem to wax and wane with low-level chemical exposure.



Claudia Miller—Chemical sensitivity is not limited to malingering workers or hysterical housewives.

When patients think they know the source of the irritant and remove it, symptoms disappear.

Once the syndrome has been initiated, a "spreading phenomenon" reportedly occurs, in which sensitivity generalizes from the original trigger to low doses of multiple, chemically unrelated substances, such as perfume, tobacco smoke, auto exhaust, and newsprint. A majority of patients also report new sensitivities to common foods, alcoholic beverages, and drugs they

have taken for years.

To explain this spreading of sensitivity, some clinical ecologists theorize that initial high-level exposure, or chronic low-level exposure to chemicals causes the immune system to overreact to subsequent exposures or to lose some of its ability to protect the body against harmful substances. The immune system, they point out, also carries out precise regulatory interactions between itself and the endocrine and nervous systems, so a dysfunctional immune system could possibly lead to a multitude of symptoms.

One study, conducted by Alan Levin, professor of immunology at the University of California at San Francisco, found that some components of immunity can be abnormal in MCS patients. He found that T-cell and B-cell counts and the ratio of helper T- to suppressor T-lymphocytes are altered in these patients. Similarly, William Rea, a clinical ecologist in Dallas, Texas, reported abnormal levels of complement, T-lymphocytes, red blood cells, and immunoglobulin G in his patients.

But research findings on immune systems of MCS patients have not been consistent; to date, no single, consistently abnormal immunological parameter has been found in these patients. Terr, for example, found normal levels of immunoglobulins, complement components, and lymphocyte subsets in a review of the medical records of 50 patients diagnosed with the disorder. Many allergists point out that formation of IgE, the immunoglobulin associated with allergy, is very specific for particular substances, such as ragweed or bee venom, and that it cannot be spread to chemically unrelated substances.

All in the Head

Now research into MCS has delved into other physiologic pathways, many of which center on nervous system interactions. One



Barry Johnson—What is not in question is that some people are in health distress.

ATSDR

University of Texas

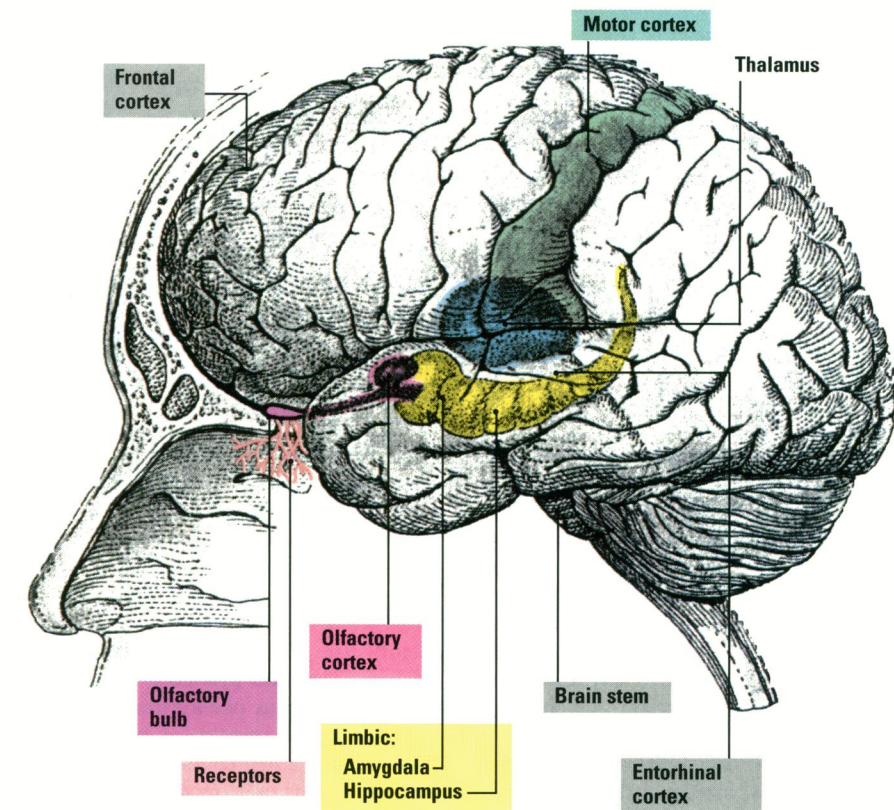
scientist, William Meggs, of the Department of Emergency Medicine at East Carolina University School of Medicine, believes that volatile organic chemicals irritate fibers in the airway, leading to inflammation, and then to systemic symptoms. The inducing exposure may alter the regulation of respiratory mucosa in such ways that subsequent chemical exposure would result in a heightened inflammatory response.

Other scientists, including two leading MCS researchers, Miller and Iris Bell of the Department of Psychiatry at the University of Arizona Health Sciences Center, are postulating an “integrated” MCS hypothesis that ties the biological and psychiatric elements of MCS together. The key, they say, is the rich neural connections that lie between the olfactory system and the limbic and temporal regions in the brain’s cerebral hemispheres, which, in part, regulate mood and autonomic functioning. They argue that many environmental chemicals gain access to the central nervous system via the olfactory and limbic pathways, inducing lasting changes in limbic neuronal activity and overall cortical arousal levels, altering a broad spectrum of behavioral and physiological functions to produce clinical MCS syndromes.

The limbic system is adjacent to the olfactory bulb, which contains nerves that are the brain’s most direct contact with the external environment; there is no protective blood–brain barrier. Each olfactory nerve consists of bipolar neurons with one end in the upper part of the nose and the other in the brain’s olfactory bulb. Odors can elicit electrical activity in the amygdala and hippocampal areas of the limbic system via this pathway. And subsensory exposure to chemicals can cause protracted, if not permanent, alterations in the electrical activity of the limbic region, beginning first with the most sensitive structures, such as the part of the amygdala that analyzes odor, says Miller.

The amygdala, the most sensitive portion of the brain to chemical stimuli, has been dubbed “emotion central,” according to Miller. It is involved in feelings and activities related to self-preservation, such as hunger and the fight-or-flight response, and it is important in regulating mood states.

Furthermore, the hippocampus, important in learning and memory, is seen by some researchers as a prime target for toxins. Damage to the hippocampus may affect the synthesis, storage, release, or inactivation of excitatory and inhibitory amino acids that serve as neurotransmitters in this area of the brain. The hippocampus also regulates body temperature, eating,



Sniffing out clues. Researchers hypothesize that environmental chemicals that gain access to the brain through the olfactory and limbic pathways may alter behavioral and physiological functions to produce MCS syndromes.

drinking, digestive and metabolic activities, aggressive behavior, and physical manifestations of emotion such as increased heart rate and elevated blood pressure. The hippocampus is also the area where the sympathetic and parasympathetic nervous systems converge. Says Miller, “Many symptoms that patients experience with food and chemical activities could be related to the autonomic nervous system.”

Bell has taken the model a step further to postulate that these systems are so intertwined that dysfunction in either can produce emotional problems or chemical sensitivity, and vice versa. “The olfactory system, hypothalamus, and limbic system pathways would provide the neural circuitry by which adverse food and chemical reactions could trigger certain neural, psychologic, and psychiatric abnormalities,” said Bell, adding that patients with chemical sensitivities have reported food cravings, binges, violence, or hypersexual activity following chemical exposure.

Bell also thinks that traumatic psychosocial events, like childhood abuse, could trigger changes in limbic activities, such as a heightened sensitivity to chemicals, that can result in MCS. She said that there is no question that the majority of MCS patients have a history of depression—many studies profiling MCS patients have pointed that out. Her own

studies of college students and the retired elderly in Tucson who have reported some sensitivity to chemical exposure have found elevated rates of “generalized distress and negative affectivity, including depression, anxiety, and irritability.” This relationship between depression and physiological symptoms is, of course, the old chicken-and-egg question. Many MCS detractors say that the depression influences the degree to which a patient rates symptoms of their malaise.

To back her theory, Bell cites interesting, albeit divergent, lines of evidence. In her surveys, she found that a self-reporting of shyness correlated most often with chemical sensitivity. And in animal models of shyness, if the amygdala is stimulated, the animal increases avoidance behavior.

Psychologists have long thought of the amygdala and limbic systems as regulators of social interaction and emotional tone, says Bell. That area of the brain is also the first place that gets information about noxious smells. If a patient acquired a vulnerability in the limbic system different from a “normal” person, he or she may be more prone to olfactory stimuli. Removal of the olfactory bulb in laboratory animals serves as a model for depression that researchers have used to test the effectiveness of antidepressant drugs, Miller says.

One study may underscore Miller and

Bell's hypothesis. To understand what symptoms MCS patients share in common, researchers at the Robert Wood Johnson Medical School in New Jersey comprehensively analyzed 11 patients considered "pure"—they had no previous physical or psychiatric conditions to explain their symptoms, nor were they under the care of a clinical ecologist or part of an MCS support group. "Therefore, they were not simply repeating patterns that had been suggested to them," says Howard Kipen, associate professor at the medical school and at the Environmental and Occupational Health Sciences Institute (EOHSI).

What Kipen and colleagues found is that none of the subjects showed medical, allergic, or immunologic abnormalities, or premorbid psychiatric conditions, but that all had an increased sensitivity to odors, and six of them had poor memory performance on functional tests which were consistent with some form of central nervous system dysfunction. What was not clear, however, was how the patient's psychological disposition (some of them were depressed and anxious) interacted with the CNS symptoms, mediated through smell. "The psyche sits on the CNS," said Kipen.

To help answer this question, Kipen will use a facility built at EOHSI for testing air pollutants to conduct studies in which MCS patients will be exposed to chemicals at such a low threshold that patients won't be able to smell them. Any

symptoms patients report will be followed by physiological tests, said Kipen.

An integral part of Bell's model are the processes by which the limbic system is sensitized, which she calls "time-dependent sensitization" (TDS) and "kindling." A TDS model "predicts that finding that either a chemical exposure event or a stressful life event at the initiation point of illness in an MCS patient increases, not decreases, the likelihood of future amplified reactivity to both chemicals and stress," said Bell. Kindling, a very specific type of TDS, is best seen when animals are given enough low levels of electrical stimuli to induce a seizure, even though the stimuli is not enough to produce a seizure on its own. Subsequently, the process becomes permanent—seizures are always produced on low voltage. An analogous phenomenon is seen in psychiatry; an important psychosocial event triggers a first episode, and the disorder then begins to be repeated with smaller and smaller events.

Bell says that animal experiments have found such cross-overs in that stress to an animal can set off neuronal sensitivity. She added that female animals have shown greater susceptibility to TDS, accounting, perhaps, for the large percentage of MCS



Iris Bell—Traumatic psychosocial events may trigger multiple chemical sensitivity.

U. of Arizona Health Sciences Center

patients who are women. Bell said that, in her view, MCS has more in common with post-traumatic stress disorder than with sick-building syndrome, to which it is usually, and erroneously, compared.

Johnson of the ATSDR calls Bell's hypothesis "fascinating, a neat theory that ties a lot of observations together." But he noted, as does Bell herself, that no specific evidence exists to support that view. "There's no animal model for MCS, and there's no federal money to create one. The few of us that work on MCS find a little money in other budgets," she said.

Johnson agrees, saying that MCS research may continue to suffer from medicine's worst vicious circle: "There are clearly people who are in distress, but in order to derive a case definition for MCS to be used by physicians to derive a diagnosis, we need to bring some science to bear on the debate, but it has been difficult to mobilize funding, because, in part, there's no case definition, nor any belief that there will be one in the near future."

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