Allergy and Multiple Chemical Sensitivities Distinguished[1]

Claudia S. Miller and Nicholas A. Ashford

When von Pirquet coined the term "allergy" in 1906, he defined it as "altered reactivity". Thus the word "allergy" as originally conceived encompassed both immunity and hypersensitivity. In 1925 European allergists influenced their American colleagues to redefine "allergy" in the context of antibodies and antigens, effectively excluding hypersensitivity on any other basis.

Forty years ago, Theron Randolph, a classically trained allergist, noted that a cosmetic saleswoman he had been seeing for rhinitis, asthma, headache, fatigue, irritability, depression, marked weight fluctuation and intermittent episodic loss of consciousness developed her symptoms following exposure to gas, oil, coal and their combustion products (Randolph, 1987, pp. 73-76). Randolph developed a diagnostic-therapeutic maneuver which consisted of removing the patient from all suspected environmental exposures and subsequently reintroducing single elements of the environment, one at a time, while observing for changes in the patient's condition (Randolph, 1960). Although what he observed in his patients appeared to be some kind of hypersensitivity, it was not allergy. Subsequently, Randolph and other physicians known as clinical ecologists published clinical descriptions of patients with polysomatic complaints, frequently including mood and cognition difficulties, triggered by a wide variety of chemical exposures, but especially petrochemical exposures, and often with concomitant food and drug intolerances. These clinical descriptions bear striking resemblance to today's MCS patients, many of whom have never heard of clinical ecology.

A review of the literature on exposure to low levels of chemicals reveals four groups or dusters of people among whom individuals with heightened reactivity have been reported (Ashford and Miller, 1989):

1. Industrial workers
2. Occupants of "tight buildings," including office workers and school-children

[1] Excerpted from Ashford, N. A. and Miller, C. S. 1991. Chemical Exposures: Low Levels and High Stakes. New York: Van Nostrand Reinhold.

3. Residents of communities whose air or water has been contaminated by chemicals
4. Individuals who have had personal and unique exposures to various chemicals in domestic indoor air, pesticides, drugs, and consumer products

These four groups are listed for comparison in Table 1. Note that they differ in professional and educational attainment, age and sex, and the mix and levels of chemicals to which they are exposed, but that all have multiple symptoms involving multiple organ systems with marked variability in the type and degree of those symptoms. Symptoms are often "subjective". For example, central nervous system (CNS) symptoms such as difficulty concentrating or irritability are common, and physical examinations are frequently unremarkable for individuals in each category.

TABLE 1
Chemically Sensitive Groups

Group	Nature of Exposure	Demographics
Industrial workers	Acute and chronic exposure to industrial chemicals	Primarily males: blue collar, 20 to 65 years old
Tight-building occupants	Off-gassing from construction materials, office equipment or supplies; tobacco smoke; inadequate ventilation	Females more than males; white collar office workers and professionals; 20 to 65 years old; schoolchildren
Contaminated communities	Toxic waste sites; aerial pesticide spraying; water contamination; air contamination by nearby industry and other community exposures	All ages, male and female; children or infants may be affected first or most; pregnant women with possible effects on fetuses; middle to lower class
Individuals	Heterogeneous; indoor air (domestic), consumer products, drugs, and pesticides	70-80 % females; 30 to 50 years old (Johnson and Rea 1989); white middle to upper middle class and professionals

Many affected individuals report a major precipitating (inducing or "sensitizing") exposure which marked the onset of their chemical sensitivities. In one survey of 6,800 persons claiming to be chemically sensitive, 80 percent asserted that they knew "when, where, with what, and how they were made ill" (National Foundation for the Chemically Hypersensitive, 1989). Of the 80 percent, 60 percent (that is, almost half of those who replied) blamed pesticides. The respondents to the survey were self selected, and the result

must be interpreted with caution. Nevertheless, the results suggest that future surveys of persons with different exposure histories and symptoms might contribute to an understanding of underlying mechanisms and causes.

In some chemically sensitive patients no single, identifiable, "high-level" exposure seems to have been associated with the onset of their difficulties. Exposures could have occurred but were not recognized or remembered. Some observers suggest that repetitive or cumulative lower level exposure events may lead to the development of sensitivities. Still others implicate genetic predisposition, pregnancy, major surgery with anesthesia, physical trauma, or major psychological stress as contributors to the illness. Based upon the increasing number of outbreaks of sick building syndrome, increased reporting of symptoms in contaminated communities to state health departments, increased recognition of problems in the industrial workplace, and the increasing numbers of physicians treating chemically related sensitivities, the existing evidence does suggest that chemical sensitivity is on the rise and could become a large problem with significant economic consequences related to the disablement of productive members of society.

The fact that the demographically diverse groups listed in Table 1 share similar patterns of illness (that is, onset after a major chemical exposure; subsequent hyperreactivity to low levels of a variety of chemicals commonly encountered in the environment such as cigarette smoke, perfume, and traffic exhaust; and multisystem complaints with frequent mood, memory and concentration difficulties) suggests that the problem may be real.

In addition, the temporal cohesiveness of onset of illness within groups of individuals sharing a recognized, major chemical exposure event, for example, the development of symptoms in several family members, co-workers or community members exposed simultaneously, help point to the problem as potentially real in those circumstances.

Although a definitive and accurate picture is yet to come, at this time these pieces-viewed collectively-provide sufficient evidence to conclude that chemical sensitivity does exist as a Serious health and environmental problem.

The different meanings of the term "sensitivity" are at least in part responsible for the confusion surrounding chemical sensitivity. In the classical, toxicological use of the word "sensitivity", those individuals who require relatively lower doses to induce a particular response are said to be more sensitive than those who would require relatively higher doses before experiencing the same response. A hypothetical distribution of sensitivities, that is, the minimum doses necessary to muse individuals in a population to exhibit a harmful effect, is shown in curve A in Figure 1-1. (If we plot the cumulative number of individuals who exhibit a particular response as a function of dose, we generate a population dose-response curve; see curve A in Figure 1-2). This distribution describes the traditional toxicological concept of sensitivity. Curve A in Figure 1-1 illustrates that health effects of classical diseases are seen in a significant portion of the normal population at a certain dose; the sensitive and resilient populations are found in the tails of the distribution.

A second meaning of the word "sensitivity" appears in the context of classical IgE-mediated allergy (atopy). IgE is one of five classes of antibodies made by the body, and is, from the perspective of classically allergic individuals, the most important antibody. Atopic individuals have IgE directed against specific environmental incitants, such as ragweed or bee venom. Positive skin tests in these individuals correlate with a rapid onset of symptoms when they are actually exposed to those allergens. The atopic individual exhibits a reaction whereas non-allergic individuals do not, even at the highest doses normally found in the environment. A hypothetical sensitivity distribution for an atopic effect is shown in curve B of Figure 1-1, and the dose-response curve derived from that distribution is found in curve B

of Figure 1-2. Allergists include in the term "allergy" well-characterized immune responses that result from industrial exposure to certain chemicals, such as nickel or toluene diisocyanate (TDI). Most allergists refer to such responses as "chemical sensitivity", and reserve this term for responses that have a distinct immunological basis, preferring to use a term such as "chemical intolerance" for nonimmunological responses to chemicals.

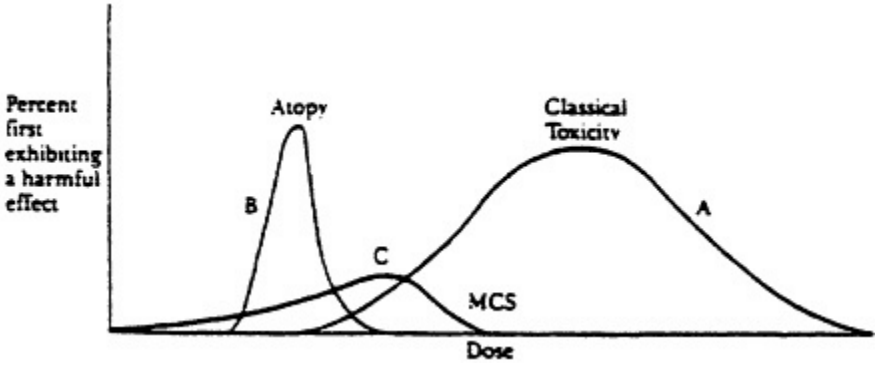

Figure 1-1 Hypothetical distribution of different types of sensitivities as a function of dose. Curve A is a sensitivity distribution for classical toxicity, e.g., to lead or a solvent. Sensitive individuals are found in the left-hand tail of the distribution. Curve B is a sensitivity distribution of atopic or allergic individuals in the population who are sensitive to an allergen, e.g., ragweed or bee venom Curve C is a sensitivity distribution for individuals with multiple chemical sensitivities who, because they are already sensitized, subsequently respond to particular incitants, e.g., formaldehyde or phenol.

Patients suffering from multiple chemical sensitivities (MCS) may be exhibiting a third and entirely different type of sensitivity. Their health problems often, but not always, appear to originate with some acute or traumatic exposure, after which the triggering of symptoms and observed sensitivities occur at very low levels of chemical exposure. The inducing chemical or substance may or may not be the same as the substances that thereafter provoke or "trigger" responses. (Sometimes the inducing substance is described as "sensitizing" and the individual affected as a "sensitized" person). Reactions may sometimes be observed at incitant levels similar to those to which classically sensitive and atopic patients respond. Unlike classical toxicity, however, here the effects of low-level exposures are not simply those effects observed in normal populations at higher doses. The fact that normal persons-for example, most doctors-do not experience even at higher levels of exposure those symptoms that chemically sensitive patients describe at much lower levels of exposure probably helps to explain the reluctance of some physicians to believe that the problems are physical in nature. (Although this also describes atopy, in this case the sensitivity is not IgE mediated). To compound the problem of physician acceptance of this illness, multiple organ systems may be affected, and multiple substances may trigger the effects. Over time, sensitivities seem to spread, in terms of both the types of triggering substances and the systems affected (Randolph, 1962, pp. 98 and 119). Avoidance of the offending substances is usually effective but much more difficult to achieve for these patients than for classically sensitive patients because symptoms may occur at extremely low doses

and the exposures are manifold and ubiquitous. Adaptation to chronic low-level exposure with consequent "masking" of symptoms (discussed more fully later) may make it exceedingly difficult to discover these sensitivities and unravel the multifactorial triggering of symptoms.

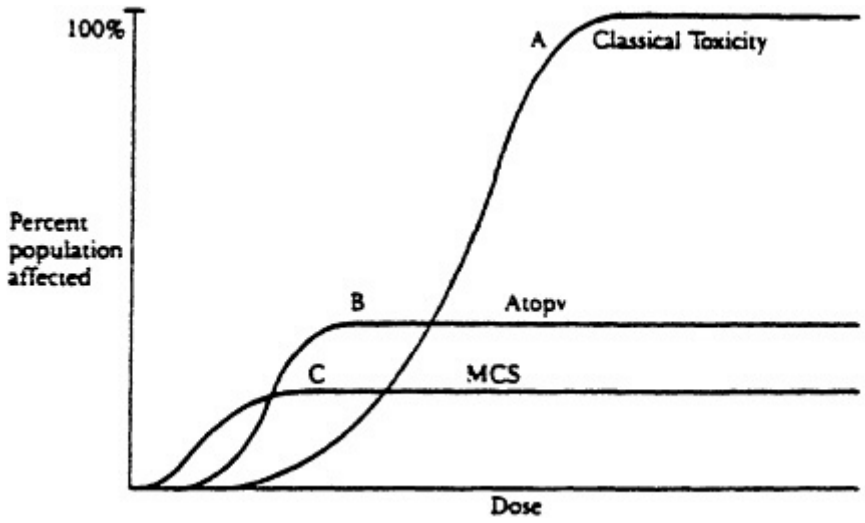

Figure 1-2 Hypothetical population dose-response curves for different effects. Curve A is a cumulative dose-response cur e for classical toxicity, e.g., to lead or a solvent. Curve B is a cumulative dose-response curve for atopic or allergic individuals in the population who are sensitive to an allergen, e.g., ragweed or bee venom. Curve C is a cumulative dose-response curve for individuals with multiple chemical sensitivities who, because they are already sensitized, subsequently respond to particular incitants, e.g., formaldehyde or phenol.

A hypothetical sensitivity distribution for a single symptom for the already chemically sensitive person in response to a single substance trigger is shown in curve C of Figure 1-1, and the corresponding dose-response curve is shown in curve C of Figure 1-2. It should be emphasized, however, that individuals who become chemically sensitive may have been exposed to an initial priming event that was toxic, as classically defined, and which was the cause for their having developed chemical sensitivities in the first place.

Conceivably, exposure to certain substances, such as formaldehyde, might elicit all three types of sensitivities.

The fact that sensitivity means something quite different to toxicologists, allergists, and clinical ecologists reflects the different disease paradigms under which each operates. Neither traditional allergists nor toxicologists fully appreciate the two-step process of induction and triggering that seems to characterize multiple chemical sensitivities.

Those clinical ecologists who reference the literature on classical chemical toxicity to buttress their case for chemical sensitivity may be adding to the confusion and contributing to others' reluctance to accept their ideas. Likewise, allergists who dismiss chemical sensitivity on the grounds that it is not consistent with a recognized immunologic mechanism may be overlooking another kind of sensitivity in their patients. Although chemicals may act in some manner (via a toxic mechanism, for instance), to predispose or cause the body to be

reactive to subsequent low-level chemical exposures, the resulting hyperreactivity to low levels of chemically diverse and unrelated substances is not toxicity as classically defined or understood at this time. Some allergists maintain that the term "chemical sensitivity" should not be used in the context we have used it here, but should be reserved only for those responses having an immunological basis. However, the term sensitivity has broader applicability. A parallel might be the word "resistance", which is widely understood whether one is talking about electricity, psychiatry, or an infectious disease. Similarly, "sensitivity" is easily understood when used in any of the three contexts illustrated in this section; it is not the exclusive property of the allergist.

Although chemically sensitive patients were first described by Randolph in the 1950's, the problem seems more prominent in the past decade or so. There are some historical developments which may have contributed to a recent increase in chemical sensitivity.

Americans today spend many more hours per day indoors at work and at home, in schools, shopping malls, and other buildings than preceding generations (Environmental Protection Agency, 1989). On the average, we spend 90 percent of our time indoors. With the concern for energy conservation following the oil embargo of the 1970's, homes and office buildings in the United States were constructed more tightly and make-up air (fresh air intake) was cut to a minimum. Similarly, homeowners and new home builders caulked and sealed, installed storm windows and extra insulation, and effectively reduced fresh air infiltration. On the average, newer homes have half as much fresh air infiltration as older homes (0.5 versus 0.9 air changes per hour) (Mage and Gammage, 1985).

Over the past decade, EPA has conducted TEAM (Total Exposure Assessment Methodology) studies on a variety of volatile organics (1980-1987), carbon monoxide (1982-1983), pesticides (1986-1989), and particulates (1987-present). Samples of 20 volatile organic compounds in the personal (indoor) air, outdoor air, drinking water, and breath of approximately 400 residents of New Jersey, North Carolina, and North Dakota were collected (Wallace, 1987).

Levels of indoor air contaminants were often many times higher than outdoor levels, and sometimes orders of magnitude higher than outdoor levels. Breath levels for most chemicals measured were 30-40 percent of indoor air levels, but measured up to 90 percent of indoor air levels in some cases-tetrachloroethylene, for example. A study of non-occupational pesticide exposure also showed dramatically higher concentrations of pesticides inside homes than out of doors (Immerman, 1990).

Remarkably, the sources of pollutants that were identified by the EPA in homes are the same ones individuals with multiple chemical sensitivities identify as provoking their often vague and seemingly inexplicable symptoms, for example, room air deodorizers, attached garages, hot showers and spas, dry cleaned clothing, cleaning agents and disinfectants.

Before World War II, U.S. production of synthetic organic chemicals totaled fewer than a billion pounds per year. By 1976, production had soared to 163 billion pounds annually (Odell, 1980). Increased sources of indoor air pollution, coupled with decreased fresh make-up air, have transformed the indoor environment. Community exposures to toxic chemicals, industrial and office exposures, and other episodic exposures of individuals also increased, reflecting the rise in production of coal-and oil-derived chemicals and synthetics.

These changes in chemical production, consumer products, and building design have been accompanied by an increasing number of people who appear to react to low levels of environmental pollutants. Interestingly, since World War II certain illnesses, such as asthma

(Sly, 1983) and depression (Klerman and Weissman, 1989), seem to have shown upsurges. It is easy to imagine that asthma could be related to chemical exposures. In the case of depression, it is recognized that solvent-exposed workers experience more depression and cognitive difficulties. Further, the majority of indoor air contaminants are solvents, albeit concentrations are generally much lower than those found in an industrial setting. Randolph often referred to chemical sensitivities as the "petrochemical problem" because the increase in the incidence of this illness seems to parallel the growth of the petrochemical industry and the increased use of synthetic materials such as particle board, pesticides, synthetic textiles, plastics, and food additives by consumers since World War II.

Randolph, who had been hospitalizing patients and testing them for their food sensitivities, found a critical element in many of his patients' recoveries was avoidance of environmental chemical exposures in their jobs and homes while in the hospital. He developed "comprehensive environmental control", a diagnostic approach in which patients avoid exposure to synthetic chemicals in order to facilitate diagnosis of chemical sensitivity.

Briefly, this technique involves placing the patient in a specially constructed environment devoid of materials that off-gas; avoiding the use of drugs, cosmetics, perfumes, synthetic fabrics, pesticides, and similar substances; and having the patient fast for a period of days until symptoms resolve. This initial period of avoidance and fasting requires approximately 4 to 7 days on the average. During this time, the patient exhibits withdrawal symptoms such as headache, malaise, irritability, or depression. By the end of this time, the patient's symptoms, if environmentally related, should dear, provided that end-organ damage has not occurred. At the end of this avoidance phase, the patient reportedly has a markedly lower pulse rate and an increased sense of well-being, as well as resolution of symptoms. Drinking waters from a variety of sources also are tested to find one most compatible with the patient. Next, individual foods are reintroduced, one per meal, over a two-to three-week period. Following this, the patient is placed on a rotating diet of "safe" foods (i.e., foods that did not provoke symptoms for that particular patient). Finally, the patient is challenged with very low levels (levels routinely encountered in daily living) of common chemicals. Those exposures, both food and chemical, that induce symptoms are to be avoided.

A description of comprehensive environmental control and its role in diagnosis and therapy first appeared 30 years ago in Clinical Physiology (Randolph, 1960) and again in the Annals of Allergy in 1965 (Randolph, 1965).

The detailed design of an environmental unit is beyond the limits of this discussion, however, some of the essentials are noted here. Although conceptually simple and scientifically elegant, achieving a well controlled environment within the average hospital is technically difficult.

First, by employing construction materials, furnishings, and clothing that are less likely to off-gas, very low levels of volatile organic compounds (for example, from synthetics) are maintained inside the unit. To create and operate a unit that is as free as possible from chemical pollution requires knowledge, precision, and vigilance while working with architects, ventilation engineers, contractors and their suppliers, nurses, dieticians, food and water suppliers, and maintenance and custodial staffs.

Several units have been operated by the clinical ecologists and one, which was patterned after those of the ecologists, was operated by John Selner, a Denver allergist. Currently none are in operation, although all of the physicians who have been involved with these units have found them to be a valuable tool for the evaluation of certain patients.

The clinical ecologists' environmental units and Selner's unit shared many of the same

design and operational parameters (Table 2). Studies from ecologists' units leave much to be desired in terms of study design. Unfortunately, no studies were ever published from the allergists' unit in Denver.

TABLE 2
Features of Environmental Units[a]

Characteristics/Practices	Allergists' Unit[b]	Clinical Ecologists' Units[c]
Construction using materials that do not off-gas (primarily glass, stell, ceramic; cotton bedding and clothing). Avoidance of synthetic materials. No perfumes, cosmetics, odorous cleaners/ soaps, etc.	Yes	Yes
Air supply filtered; patients' rooms under positive pressure to reduce contamination from adjacent areas; airlocks	Yes	Yes
Patients' medications discontinued insofar as possible; gradual withdrawal from steroids, etc.	Yes	Yes
Patients fasted for 4 to 8 days to clear symptoms.	Yes, if symptoms do not clear after several days in unit	Yes at time of admission to unit
Organic foods used for food testing; commercial foods tested also	Yes	Yes
Patients tested for acceptable water	Yes	Yes
Challenges performed using single foods and chemicals after period of avoidance (to eliminate masking)	Yes	Yes

[a] None of the units described in this table is currently in operation.
[b] Selner in Denver (Selner and Staudenmayer, 1985).
[c] Randolph in Chicago and Rea in Dallas.

By isolating his patients from their usual environments and then re-exposing them to various foods and chemicals one by one, Randolph observed that adaptation seemed to play an important role in his patients' responses to many common substances they ate, drank or inhaled. Adaptation is known in other contexts as "acclimation" or "acclimatization", "habituation", "developing tolerance" and even "addiction". Randolph used the terms "adaptation" and "addiction" most often. However, reference to one of the other words may make it easier to grasp the concept. "Acclimatization" is a widely used term in occupational health that refers to workers gradually becoming accustomed to exposures on the job, for example, heat stress. Understanding adaptation is important for two reasons: (1) adaptation may interfere with the discovery of the effects of a particular exposure on the body and (2) chemical exposures may adversely impact adaptation mechanisms and thus lead to illness.

That human beings respond to chronic exposure to environmental challenges by adapting, acclimating, acclimatizing, or even becoming addicted is widely recognized for a variety of substances. Most would agree that the use of narcotics, alcohol, nicotine, and even caffeine can be addicting. For example, the first cigarette ever smoked might be associated with eye and throat irritation, but over time, with more cigarettes, most individuals adapt, and primarily the pleasurable effects of nicotine on the brain are experienced. After months or years, more cigarettes (or alcohol or caffeine or drugs) may be required for the same amount of lift. The individuals may exhibit addictive behavior, seeking cigarettes more frequently. Subsequently, quitting cigarettes (or alcohol, caffeine, or drugs) may lead to withdrawal symptoms including irritability, drowsiness, fatigue, moodiness, and headache. The reformed smoker may become extremely intolerant of the smoke of others, even in tiny amounts. Suddenly recalled are the irritation and unpleasant feelings associated with the first cigarette ever smoked. Over time the individual had "adapted" to those effects. Adaptation, which on the surface would seem good for the organism, may in fact be a two-edged sword. Developing tolerance for the noxious properties of the exposure may allow the individual to remain in the exposure more comfortably while other harmful consequences of the exposure continue. Thus the heavy smoker who is "adapted" to tobacco smoke is at increased risk for developing emphysema, lung cancer or vascular disease. While often occurring at much lower levels of exposure than the above examples, food and chemical adaptation and addiction have been observed by some physicians in their patients. ha the case of MCS patients, *multiple* incitants, not only tobacco smoke, may be involved and *all* may need be avoided simultaneously for improvement to occur. Thus, frequent exposure to a substance results in adaptation (irritation and other warning signals may disappear). Continued exposure may lead to addiction. Reduction or cessation of exposure generally results in withdrawal symptoms.

What may confuse patients and practitioners is that the symptoms for which the individual is most likely to seek a physician's help are those that occur during withdrawal when the person is no longer exposed (or is less exposed) to the offending agent. Thus headaches may occur when the individual smokes fewer cigarettes than usual or drinks less caffeine. Indeed, these unpleasant withdrawal symptoms may be forestalled by smoking another cigarette or taking another drink of coffee, thus perpetuating addiction. Patients may report that smoking a cigarette or drinking a cup of coffee in the morning (after 8 or so hours without) relieves their headache (a withdrawal symptom) and they feel better, not suspecting that the cigarette or coffee might also be the cause of their headache.

Occupational health presents many examples in which acclimatization, inurement, or tolerance to a substance is known to develop, for example, exposure to ozone, nitroglycerin,

and solvents. Note that the incitants mentioned thus far are all quite different from one another: some are ingestants, others inhalants; some are solid, others liquid or gaseous in form; some are simple molecules, whereas others are complex mixtures. The point is that the human body appears able to adapt to an endless array of substances.

By isolating MCS patients from their usual environments and then re-exposing them to various foods and chemicals one by one, physicians have observed that many common substances patients eat, drink or inhale seem to provoke symptoms.

A biphasic response to some of these substances (Figure 2) has been reported. Initially the individual might experience a stimulatory effect (adapted response; tolerance develops) lasting varying periods of time depending upon the incitant. However, this "up" phase was generally followed by a withdrawal phase (maladapted response; loss of tolerance). Upon beginning to experience unpleasant withdrawal symptoms, the individual would seek, consciously or unconsciously, more of the same substance. These ups and downs follow a sort of sinusoidal (biphasic) pattern, as depicted in Figure 2. On the graph, beginning at zero, the patient is free of symptoms and at baseline health status. Following a one-time or occasional exposure to a provoking substance, stimulatory effects result; after a period of time (minutes to hours to days, depending upon the nature of the incitant), the stimulatory effects subside and give way to withdrawal symptoms. The frequency of these up and down reactions depends upon the frequency of exposures, and the amplitude of the stimulatory and withdrawal portions of the reaction depend upon the substance and the individual's susceptibility (degree of adaptation or addiction) to it. The particularly sensitive person exhibits larger amplitudes than the normals. The key to understanding multiple

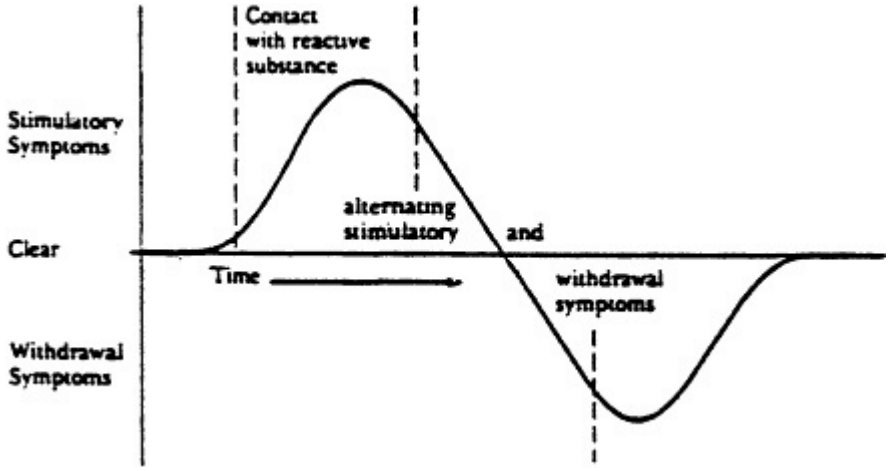

Figure 2 Symptom progression of a single reaction to an incitant. During the early phases of exposure to a particular substance, stimulatory symptoms predominate ("up," "hyper," "jittery"). As exposure to the offending agent continues, adaptation occurs and fewer of these symptoms are experienced. With removal from (or discontinuance of) exposure, the individual experiences withdraw symptoms ranging in intensity from mild to severe. (From O'Banion, D.R., Ecological and Nutritional Treatment of Health Disorders, 1981, p. 68. Courtesy of Charles C. Thomas, Publisher, Springfield, Illinois.)

chemical sensitivity may lie in recognizing these ups and downs that appear to occur after exposure to many different substances. The amplitude of a reaction varies from person to person and incitant to incitant, but the pattern is reported to be quite constant.

After long-term exposure to a given incitant (for instance, alcohol), especially in certain sensitive individuals, the degree and duration of stimulation may become less and less while the withdrawal or depressed phase becomes deeper and more prolonged. At face value, this sinusoidal reaction to a substance might seem a somewhat artificial construct, but Randolph asserts it is not.

Chemical sensitivities may be difficult to assess while a patient remains at home or even in most hospitals because these places generally contain background low levels of natural gas, disinfectants, perfumes, cleaners, tobacco smoke, paints, varnishes, adhesives, and other substances. The patient's symptoms may be masked by the presence of these contaminants.

Under normal living circumstances, the stimulatory and withdrawal levels for foods and chemicals overlap each other (Figure 3) so that in real life-outside an environmental unit-at any given moment what the organism may be feeling is a summation of all effects, whether stimulatory or depressive, of all substances recently inhaled, contacted, or ingested. Figure 3 illustrates that attempts to identify the effects of single substances would be frustrated by the overlapping responses. Only by placing the individual in an environment devoid of chemical and food incitants would one be able to determine whether the illness is alleviated. Assuming the patient improves (which occurs in the majority of cases, according to ecologists), the next step would be to reexpose the person to individual substances in order to avoid overlapping responses, and then to observe the result. If all possible food and chemical contributors are not removed, an effect may be missed. Hence, in order to rule out environmental illness definitively, an environmental unit would be required. Conceivably environmental illness could be ruled in on an outpatient basis, but not ruled out.

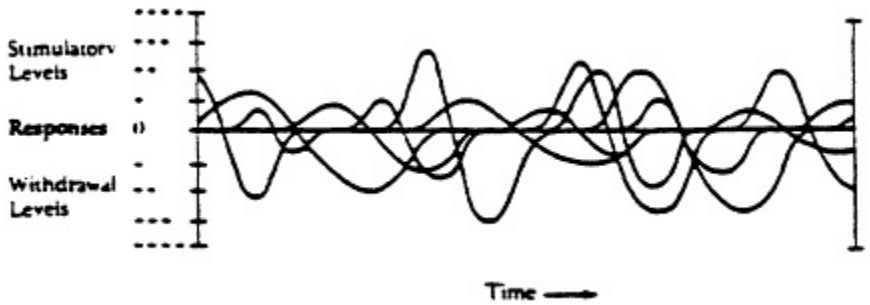

Figure 3 Overlapping of responses to food and chemical incitants in an individual with multiple exposures and multiple chemical sensitivities.

In real life, stimulatory and withdrawal reactions are observed but often not understood. For example, an asthmatic might feel well after spending a week on a Carribean island, breathing relatively uncontaminated air and eating a diet devoid of usual foods, only to have a severe, life-threatening asthmatic response to exhaust from the engine of a boat taking the individual home. Once back home in a metropolis, the asthmatic

readapts, acclimatizes to auto exhaust, combustion products and other air pollutants in the area, and experiences only chronic wheezing. Thus, following deadaptation (removal from incitants), the individual exhibits a more acute and convincing reaction upon reexposure. This appears to be what occurs in an environmental unit during testing. So acute and convincing are some of these reactions that patients themselves erroneously (at least in the eyes of some) surmise they must have an "allergy" to a particular substance. However, if the patient is not deadapted (unmasked) when tested, a reaction may not occur, convincing the physician that the "allergy" was all in the patient's mind.

Occupational health has several widely recognized examples of adaptation that are analogous (Ashford and Miller 1991). They, too, fit a biphasic pattern. Industrial hygienists and occupation health physicians know that one of the most valuable clues to work-related illness is a history of intense symptoms following return to work after a vacation or weekend (leading to withdrawal and deadaptation).

Ozone, an air pollutant of special concern to residents of Los Angeles and other cities, has been the focus of considerable research relevant to adaptation. Intrigued by how little respiratory illness and death occurred relative to the high levels of ozone in very polluted cities and suspecting adaptation might play a protective role, Hackney and associates (Hackney et al., 1977a) compared the responses of four Canadians (not adapted) and four Californians (adapted) to ozone challenges. Although reactivity varied greatly from individual to individual, Californians were only minimally reactive to levels that for the Canadians caused coughing, substernal discomfort and airway irritation, pulmonary function test decrements, and increased red blood cell fragility.

In another experiment, six volunteers with respiratory hyperreactivity were placed in an environmental chamber with ozone at 0.5 ppm (parts per million), typical of high ambient levels, for 4 days (Hackney et al., 1977). Five of six had decreased pulmonary function during days 1 to 3, but gradually improved almost to baseline by day 4, suggesting adaptation had occurred. The authors note that not all adverse effects of ozone may be prevented by adaptation; for example, increased red blood cell fragility may persist. Therefore, adaptation or masking of some symptoms may occur while other physiological alterations continue.

Individuals' abilities to adapt to ozone appear to depend upon their initial sensitivity to it. More sensitive persons adapt more slowly and cannot maintain the adaptation as long; they usually remain adapted less than 7 days following cessation of exposure (Horvath, 1981). While nitroglycerin and ozone adaptation (and deadaptation) may differ in certain respects from the adaptation (and deadaptation) described in MCS patients, solvents are among the chemicals most frequently implicated by chemically sensitive patients who attribute the onset of their illness to a particular exposure (Terr, 1989; Cone et al., 1987) and adaptation to solvents has also been documented. Vapors from various solvents are the most prevalent of indoor air contaminants (Molhave, 1982). The volatile organic compounds (VOCs) associated with sick building syndrome are in large part solvent vapors. The sensory irritation, headache, drowsiness, and other symptoms noted by occupants of tight buildings are consistent with known effects of solvent vapors, albeit at much higher concentrations.

Those who have painted or used solvents to any major extent are well aware of the olfactory fatigue (nasal adaptation) that occurs and may have experienced the stimulatory and depressive properties of solvents. Alcoholic beverages contain the solvent ethanol, which has related and familiar stimulatory and withdrawal effects.

Studies of xylene, one of the most prevalent solvents in indoor air, demonstrate that its effects are attenuated as exposure continues, presumably due to adaptation (Riihimaki and

Savolainen, 1980). Riihimaki aid Savolainen exposed healthy male volunteers to constant (100 or 200 ppm) and varying (200 or 400 ppm hourly peak) concentrations of xylene, adjusting baseline concentrations in the latter case so that a mean concentration of 100 or 200 ppm was maintained. Exposures occurred over a six-hour period (with a one-hour break at noon) for five days, followed by a two-day weekend and one to three more days of active exposure to xylene. A variety of psychophysiologic parameters were measured, inducting reaction time, body balance, manual dexterity, and nystagmus.

Of particular interest, Riihimaki and Savolainen (1980) observed that most of the adverse effects of xylene upon their normal subjects "tended to disappear after a few succeeding days of exposure." However, "after the weekend away from exposure, the effects were again discernible." They conclude: "This phenomenon suggests that tolerance had developed over a few days with regard to psychophysiological effects by xylene."

With regard to patients with chemical sensitivities who also develop dietary intolerances, Bell notes that "foods are not only sources of nutrients, but also complex mixtures of organic chemicals. For instance, it is the unique pattern of chemical constituents that make a tomato a tomato rather than an apple" (Bell, 1982, pp. 35-36). Interestingly, limonene and pinene which are present in oranges also are constituents of room air deodorizers which provoke symptoms in some chemically sensitive patients. Like airborne pollutants, foods contain a wide range of chemical constituents and are in intimate contact with the organism for long periods of time. The surface area of the gastrointestinal tract is enormous, and the chemical load, in terms of both quantity and diversity of exposure, is huge.

We have mentioned a amber of exposures that are recognized as involving adaptation. What is clear is that individuals with or without multiple chemical sensitivities undergo adaptation to a wide variety of substances in their environment. What is not dear is the specific role adaptation plays in the dramatic responses patients with food and chemical sensitivities have to low-level exposures that do not overtly affect others. These concepts are familiar to occupational health practitioners and industrial hygienists because they observe such effects firsthand among workers exposed to chemicals. Randolph states that most physicians see patients long after adaptation has occurred and at the time when end organ damage is setting in: "It is much as if the physician arrived at the theatre sometime during the last scene of the second act of a three act play-puzzled by what may have happened previously to the principal actor, his patient" (Randolph, 1962, p. 7). Through comprehensive environmental control (that is, an environmental unit), one may be able to overcome the masking effect of adaptation and back up or reverse the exposure to allow monitoring of toxicity in progress. The environmental unit may represent a kind of *dynamic toxicology*; traditional medical approaches provide only a snapshot ofwhat is happening to the patient.

There are several reasons why deadapting patients is critical to the study and diagnosis of MCS:

1. People are often exposed to dozens of different incitants simultaneously (such as volatile organic compounds in a tight home or building) and literally hundreds of different incitants over the course of a single day, so that health effects of these exposures may overlap, making it difficult to discern cause-and-effect relationships.
2. With continuous or frequent exposure to the same substance or chemically-related substances (such as xanthines in coffee, tea, chocolate and colas), individuals adapt or, in other words, develop tolerance to those exposures. Acute symptoms gradually may give way to chronic symptoms that bear no apparent

relationship to any particular exposure. Exposures may never stop long enough for the patient to reach baseline.

3. Exposures that are initially pleasant or stimulating (such as alcohol, solvents, or nicotine) generally also have withdrawal effects such as headache, depression or irritability, associated with them. Such withdrawal symptoms may occur hours to a few days after cessation of, or reduction in, exposure, greatly confounding attempts by patients and physicians to relate symptoms to a particular incitant.

Comprehensive environmental control, that is, use of an environmental trait, can overcome the masking effect of adaptation and the problems of overlapping exposures that result in overlapping responses to multiple agents. The environmental unit can back up or reverse the experience of adaptation and allow the investigator to monitor toxicity in progress. Figure 4 graphically depicts the changes in symptoms that might occur in a patient after entering an environmental unit. The advantages dynamic toxicology of this nature has over conventional methods for determining toxicity include facilitating detection of subclinical, prepathological effects of chemicals and providing more than just a snapshot of an individual's response to substances. Removing the person from interacting, time-dependent stimuli in this way allows the unraveling of multiple causes. The environmental unit is an essential tool. Many carefully conducted studies of chemical effects that have had negative or equivocal outcomes in the past may have been flawed by their failure to take adaptive mechanisms into account. The potential consequences of such an oversight are major.

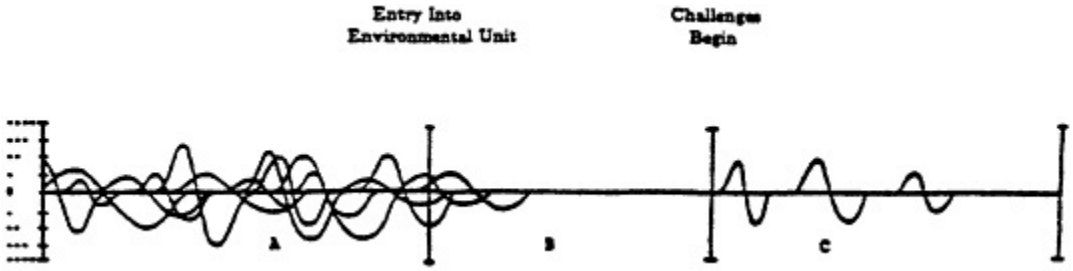

Figure 4 Graphical representation of an individuals symptoms before and after entering an environmental unit. In time period A an individual is responding to multiple incitants encountered in normal daily living (chemicals and/or foods), with stimulatory and withdrawal effects that overlap in time. At any particular time, how the person feels is determined not only by ongoing exposures, but by previous exposures whose effects may still be waning. In time period B, the individual enters an environmentally controlled facility, fasting. With cessation of contributory exposes, withdraw effects occur, for example, headache, fatigue, and myalgias. Symptoms continue for some time (typically for 4-7 days) until the individual reaches "0" baseline. In time period C, single challenges to suspected incitants are administered. Symptoms, often robust, develop soon after challenges, allowing patient and physician to begin to observe the cause-and-effect relationship between exposures and symptoms for that individual.

Important questions that must be addressed in future studies of chemical sensitivity include:

1. Are subjects in a deadapted state prior to challenges so that extraneous

exposures during and prior to a challenge (up to several days before) do not interfere with testing?

2. Are open challenges performed first to confirm that the placebo (clean air or a masking odor such as peppermint) is in fact a placebo and that the "active" challenge is something to which the patient has had demonstrable reactions?
3. What is the recency and latency of the patient's exposure to the substance being tested? In other words, has enough time elapsed (about a week or so) that the person is no longer adapted or reacting to the last exposure but not so much time that the sensitivity has waned? Recency of exposure is recognized as a crucial variable in conducting challenges in patients with occupational asthma, for example.

The rift between allergy and clinical ecology has been fueled by the difficulty inherent in communicating these complex observations concerning adaptation, with unfortunate consequences for patients. An ancient proverb observes "When elephants fight, it is the grass that suffers". When physicians are embattled, it is the patient who suffers. Carefully designed studies of deadapted patients in an environmental unit, using double-blind placebo-controlled challenges, are an essential first step for helping resolve current professional antagonisms and placing research in this field on scientific footing.

SUMMARY OF ADAPTATION HYPOTHESES

Symptoms of exposure to many chemicals, whether inhaled or ingested, appear to follow a biphasic pattern. Adaptation is characterized by acclimatization (habituation, tolerance) with repeated exposures that result in a masking of symptoms. Withdrawal occurs when exposure is discontinued. Once a person has adapted, then the experimental consequences are that further exposures have very little additional effect and therefore may not be observed. The observer may not be able to witness the stimulatory or reactive event because a kind of "saturation" effect has set in.

Adaptation and withdrawal occur for a wide variety of organic and inorganic substances in many physical forms, including various dusts and fumes, solvents, nitroglycerin, ozone, drugs and foods.

An individual is exposed to a variety of substances at different times with varying frequency, duration, and intensity of exposure for each of these substances and with varying frequency and duration of reduction in or cessation of exposure for each substance. The individual may be in different stages (stimulatory or withdrawal) simultaneously for different substances. These stages may overlap and interfere with attempts to observe cause-and-effect relationships.

Adaptation may mask some symptoms or effects while other physiological alterations may continue.

Comprehensive environmental control, that is, use of an environmental unit, can overcome the masking effect of adaptation and the problems of overlapping exposures that result in overlapping responses to multiple agents. The environmental unit can back up or reverse the experience of adaptation and allow the investigator to monitor toxicity ha progress. The advantages dynamic toxicology of this nature has over conventional methods for determining toxicity include facilitating detection of subclinical prepathological effects of chemicals and providing more than just a snapshot of an individual's response to substances. Removing the person from interacting, time-dependent stimuli in this way allows the unraveling of multiple causes.

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