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Review article

Mechanisms of multiple chemical sensitivity

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Dedicated to the late Philip Chambers

Abstract

Sensitivity to chemicals is a toxicological concept, contained in the dose–response relationship. Sensitivity also includes the concept of hypersensitivity, although controversy surrounds the nature of effects from very low exposures. The term multiple chemical sensitivity has been used to describe individuals with a debilitating, multi-organ sensitivity following chemical exposures. Many aspects of this condition extend the nature of sensitivity to low levels of exposure to chemicals, and is a designation with medical, immunological, neuropsychological and toxicological perspectives. The basis of MCS is still to be identified, although a large number of hypersensitivity, immunological, psychological, neurological and toxicological mechanisms have been suggested, including: allergy; autosuggestion; cacosomia; conditioned response; immunological; impairment of biochemical pathways involved in energy production; impairment of neurochemical pathways; illness belief system; limbic kindling; olfactory threshold sensitivity; panic disorder; psychosomatic condition; malingering; neurogenic inflammation; overload of biotransformation pathways (also linked with free radical production); psychological or psychiatric illness; airway reactivity; sensitisation of the neurological system; time dependent sensitisation, toxicant induced loss of tolerance. Most of these theories tend to break down into concepts involving: (1) disruption in immunological/allergy processes; (2) alteration in nervous system function; (3) changes in biochemical or biotransformation capacity; (4) changes in psychological/neurobehavioural function. Research into the possible mechanisms of MCS is far from complete. However, a number of promising avenues of investigation indicate that the possibility of alteration of the sensitivity of nervous system cells (neurogenic inflammation, limbic kindling, cacosomia, neurogenic switching) are a possible mechanism for MCS.

Keywords: Sensitivity; Low levels chemical exposures; Chronic fatigue; Multiple chemical sensitivity

1. Introduction

"Disease" can be a pathologic process, and not all persons with a disease are ill. Symptoms of illness associated with a disease may be manifest or persist after the disease has disappeared. Many factors, including personal characteristics and social circumstances, can be responsible for sensitivity to, and recovery from, disease and illness (Cluff, 1991). There are many different neurological and psychiatric syndromes that follow acute illness, but their clinical pictures and pathogenesis are poorly understood.

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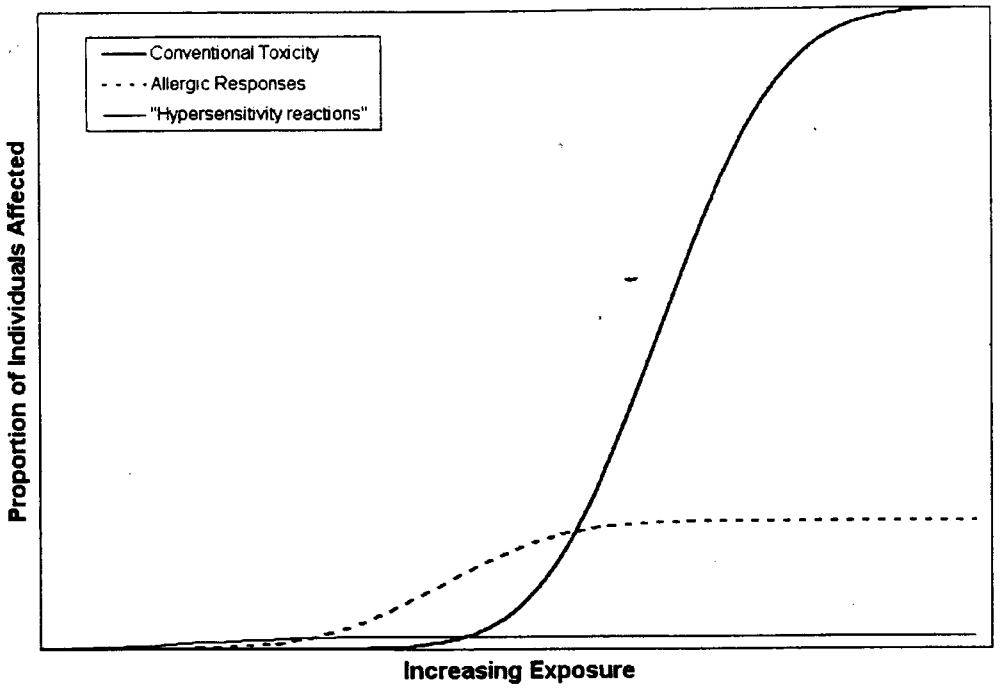

Fig. 1. Dose–response relationships for different toxic endpoints.

One such condition that has received attention over the past decade is the issue of low level chemical exposures and the effects they may cause. While conventional toxicological concepts can explain the effects of elevated toxic exposures, the issue of effects from low level exposures is a relatively new area of study.

One of the problems in dealing with a toxic material is that if dose–response information is available, it usually refers to high level exposures at the upper end of the relationship, as effects are more likely to be evident. However, an absence of effect is usually not considered to be very informative. Indeed, in the absence of appropriate dose–response information, an absence of effect should not be concluded as being the effect of absence. An important emerging area of toxicology is the investigation of the biological effects of low level exposures (BELLE), that is, effects at the lower end of the dose–response relationship (Calabrese, 1992, 1994; Davis and Calabrese, 1998).

Historically, a syndrome called neurasthenia or "American nervousness" was described in 1880, which has many features of chemical sensitivity. Modern attempts to deal with the "chemical susceptibility problem" began in the 1950s, with the original work of Randolph (1962). A model of chemical sensitivity was proposed, consisting of the inability of the body to adapt to chemicals, and the development of responsiveness to extremely low concentrations after sensitisation in the mid-1950s. Early research investigated food intolerances.

The numbers of cases of people with such a chemical sensitivity continues to grow, and the possible mechanisms that might underlie such a condition will be described in this article.

1.1. The dose–response relationship

The relationship between dose and response forms the basis of one of the fundamental toxicological principles, the dose–response relationship (see the thick curve in Fig. 1). That is, as dose (or exposure) increases, the proportion of affected individuals (or the intensity of the effect) in-

creases. This curve can be used to explain most toxicological phenomena (WHO, 1978).

As well as conventional responses to toxic exposures, it is also recognised that some people (perhaps up to 10–20% of the population) can show allergic responses to lower levels of chemical exposures (as shown in the dashed line in Fig. 1). Allergy is a particular type of toxic response, mediated through the immune system. Individuals showing allergic reactions are generally predisposed to such responses, the predisposition often being genetically based. Further, these responses can be identified through measures of immunological or allergic function.

However, a third category of response exists, in an even smaller group of people (maybe 0.5–2% of the population) of a hypersensitivity or idiosyncratic sensitivity to chemicals at very low exposures, for which physiological or medical indicators are not yet available (shown in the thin line in Fig. 1). The terms hypersensitivity and idiosyncratic describe separate responses. The individual who is exposed to, for example solvent chemicals, can show a range of signs and symptoms. Solvents produce effects in a range of body systems, for example, the nervous system, liver and kidneys, but not in other body systems, for example, in the skeletal system. It could be concluded that an individual showing symptoms of toxicity in the nervous system (for example, neurobehavioural effects) at low exposure to solvents was hypersensitive, as the nervous system is a target organ. However, symptoms of toxicity in the skeletal system from solvent exposure are more likely be an idiosyncratic response because solvents do not normally affect the skeleton. For this reason, it should be concluded in hypersensitivity responses not that the possibility of such symptoms is remote, but that the dose–response relationship needs to be shifted to the left to take into account such effects.

Lastly, because the dose–response relationship is based on the normal distribution (or at least the log normal distribution), any such relationship approaches zero asymptotically. Arguments that inclusion of chemical sensitivity and hypersensitivity effects require a paradigm shift (Staudenmayer, 2001) or lack evidence of a threshold (Doull, 1996) are unnecessary. Given a sufficiently large population, it is possible that hypersensitive individuals are part of a very long tail approaching zero on the conventional dose–response curve.

1.2. Types of chemically sensitive individuals

It is customary to call the individual who responds adversely to low exposures to chemicals as being "sensitive". While a chemically sensitive individual may arise in any group of individuals, there are four main types who contain individuals in which heightened reactivity to chemical exposures has been reported:

- industrial workers who are exposed occupationally to chemicals as part of their daily activities;
- office workers working in tight buildings;
- individuals who may be located in areas of contamination (such as contaminated sites or close to known sources of pollution); and
- individuals who, for one reason or another, received an unexpectedly debilitating exposure to a chemical.

Table 1 (modified from Ashford and Miller, 1991) outlines the exposure conditions and demographics of these groups.

Although the condition that affects the individual who is sensitive to low exposures to chemicals was known by a variety of terms for many years (including environmental illness, hypersensitivity syndrome, twentieth century disease, total allergy syndrome, ecological illness and chemical sensitivity problem (Sandler, 1993)), the name multiple chemical sensitivity (MCS) was introduced in the late 1980s, when the first articles on MCS were published (Cullen, 1987; Hilleman, 1991).

Until that time, there was a lack of a clear definition as to what MCS was, as several medical specialities squabbled about whether MCS was a medical condition, and if so, how it could be diagnosed. Some of the more divisive infighting has been between the allergists and immunologists on one side and the clinical ecologists on the other. This controversy made it difficult for patients to find objective information about the issue, and impeded their ability to resolve MCS-

Table 1
Chemically sensitive groups

Group	Nature of exposure	Demographics
Industrial workers	Acute or chronic exposure to industrial chemicals.	Primarily males. 20–65 years old.
Office workers (in "tight buildings")	Inadequate ventilation. Off gassing from construction or refurbishment materials or from office equipment. Tobacco smoke.	More females than males. White collar workers. 20–65 years old. School children.
Contaminated communities	Toxic waste sites. Contamination by nearby industry sites. Aerial pesticide spraying. Groundwater contamination. Other community exposures.	Middle to lower class. All ages, male and female. Children or infants affected first or most, possible effects in pregnant women.
Individuals	Heterogeneous. Indoor air (domestic). Pesticides, consumer products and drugs.	White upper to middle class, primarily females, 30–50 years old.

related problems at the workplace, insurance or litigation levels. However, the name MCS is now well established (Cullen, 1997), although debate about whether MCS is a real disease continues in some sectors of the health care profession.

Later, MCS-like conditions have also been reported, such as Gulf War Syndrome (Reid et al., 2001) and Aerotoxic Syndrome (Winder and Balouet, 2000).

2. Multiple chemical sensitivity

2.1. Diagnosis of MCS

Conditions in which physical symptoms are unsupported by physical findings and have diagnostic labels that describe the disorder without indicating either cause or pathology are especially troubling for the medical practitioner. However, a working definition for MCS was established in 1987 (Cullen, 1987). This definition, subsequently modified, suggested a grouping of effects in workers who had been exposed to low levels of several chemicals. A Symposium on MCS was held by the Association of Occupational and Environmental Clinics (AOEC) in the USA in 1991 which proposed a "research definition" for MCS for the purposes of epidemiological study (Rest, 1992):

- a change in health status identified by the patient (which rejects the notion of an association with a single event, but permits patients to identify some time period in which they felt well and a subsequent time period when they did not);
- symptoms triggered regularly by multiple stimuli;
- patients must have symptoms or signs related to chemical exposures at levels tolerated by the population at large;
- symptoms must have been experienced for at least 6 months;
- a defined set of symptoms reported by patients;
- symptoms that occur in three or more organ systems;
- exclusion of patients with other conditions (not all psychiatric conditions were necessarily considered exclusionary).

It has been suggested that this definition is overly restrictive. However, this is a research definition, and researchers must be careful not to study a diverse group of individuals who could have several different illnesses. It is possible that patients who do not satisfy all the criteria in the definition may still have MCS, and it is probable that the definition will be made less stringent once research better delineates the condition. However, there can be little doubt that a patient satisfying all criteria can be considered as suffering from MCS.

Criteria for diagnosis of MCS have been modified, and the following consensus criteria for the diagnosis of MCS were suggested in 1999 (Nethercott et al., 1993; Bartha et al., 1999):

1. The symptoms are reproducible with [repeated chemical] exposure.

2. The condition is chronic.
3. Low levels of exposure [lower than previously or commonly tolerated] result in manifestations of the syndrome.
4. The symptoms improve or resolve when the incitants are removed.
5. Responses occur to multiple chemically unrelated substances.
6. Symptoms involve multiple organ systems.

Therefore, the debate about MCS has moved from a discussion as to whether it exists, to how it can be defined, diagnosed and studied.

2.2. Symptoms of MCS

As a group, people suffering from MCS have a large number and range of symptoms they associate with chemical exposures. The complaints are physical and mental and involve nearly all systems of the body. The commonest symptoms include:

- respiratory symptoms;
- headache;
- fatigue;
- flu-like symptoms;
- mental confusion;
- short term memory loss;
- gastro-intestinal tract difficulties;
- cardiovascular irregularities;
- genito-urinary problems;
- muscle and joint pain;
- irritability and depression;
- eye, ear, nose and throat problems.

This list is not meant to be exhaustive and other symptoms, such as polyuria, have been reported.

This huge range of symptoms has meant that some medical practitioners have dismissed chemical sensitivity as a real medical condition because it cannot be diagnosed, preferring to suggest immunological, neurological or psychological alternatives (sometimes as a means of getting rid of the patient). In any event, management of the MCS patient is problematic (Weaver, 1996).

The basis of MCS is still to be identified, although a range of hypersensitivity, immunological, psychological, neurological and toxicological mechanisms have been suggested (see Table 2, based on Wolf, 1994; Sparks et al., 1994; Fiedler and Kipen, 1997 and the references cited in the table). Debate continues as to whether symptoms are an organic response to real exposures, or a psychological response to perceived exposures (Pirages and Richard, 1997).

Most of these theories tend to break down into concepts involving:

- disruption in immunological/allergy processes;
- alteration in nervous system function;
- changes in biochemical or biotransformation capacity; and
- changes in psychological/neurobehavioural function.

Research into the possible mechanisms of MCS is far from complete (Ashford and Miller, 1992). There has been criticism that current principles of toxicology, immunology and allergy do not provide a coherent explanation of chemical sensitivity (Weiss, 1994; Bronstein, 1995; Labarge and McCaffrey, 2000). However, a number of promising avenues of investigation indicate that the possibility of alteration of the sensitivity of nervous system cells (neurogenic inflammation, limbic kindling,[1] cacosomia, neurogenic switching) may be a

[1] The limbic system is part of the deeper structures of the central nervous system, which, in evolutional terms is an older part of the brain. It was initially considered that the limbic system processed olfactory information in humans, but the sense of smell is less important in humans and the limbic system almost certainly is involved in processing other sources of information as well as olfactory inputs. Whereas in humans the hypothalamus is involved in automatic body functions, and the cortex is involved with higher mental performance, one function of the limbic system is to control expression of the emotions, especially some of the stronger emotions (such as avoidance behaviour, parenting behaviour, rage or sexual behaviour). From a biological viewpoint, the emotions act by directing behaviour into specific patterns. For example, rage behaviour produces a different set of behavioural responses than say, fear behaviour or sexual behaviour. Further, while many of the patterns of such behaviours are "hard wired" through evolutional processes and are now part of the repertoire of human behaviour, others can be altered through learning. If the limbic system can "learn" to react to a specific stimulus by modifying a pre-existing behavioural pattern or developing a new pattern of behaviour, then the production of such responses will become more efficient as the process of responding to the stimulus is incorporated into memory. This learning process means that the initiation of the response to the stimulus will become more efficient—it will take less time or require less of a stimulus. This is the basis of limbic kindling.

Table 2
Possible mechanisms for MCS

Mechanism	Comment
Airway reactivity	Rhinitis and airway reactivity are common symptoms in MCS sufferers (Meggs and Cleveland, 1993). The MCS symptom complex is also seen in patients with asthma or rhinitis following acute exposure to chemicals in a condition called "reactive upper airway dysfunction syndrome" (Meggs, 1995a).
Allergy	Most allergic reactions have underlying immune mechanisms that have correlates that can be measured clinically. These correlates are rarely found altered (or only mildly altered) in MCS sufferers, suggesting that MCS is not mediated through allergic mechanisms. However, allergy and chemical sensitivity may be associated (Ross, 1997).
Anxiety reaction	Clinical observation of MCS sufferers challenged with their trigger substances report symptoms and signs consistent with an anxiety reaction with hyperventilation (Leznoff, 1997).
Autosuggestion	Belief that disease (and its causes) exist may be the cause of symptoms. Further, such a belief is perpetuated and reinforced by support groups, medical advisers and the media. Unlikely as a possible cause as many MCS sufferers must make massive lifestyle changes against pre-existing belief systems.
Cacosomia	Altered olfactory sensitivity (Schusterman et al., 1988). The smell of chemicals may produce autonomic arousal, which becomes amplified with time (Dalton et al., 1997; Bell, 1996). Also may be seen as odour mediated panic attacks.
Conditioned response	This theory suggests that smelling the chemical causes behavioural responses, which produces the symptoms (Bolla-Wilson et al., 1988). The basic mechanism is Pavlovian conditioning (Seigel, 1998). However, the reverse is often the case—most MCS sufferers recognise symptoms first and then find they have been exposed.
Hope scores	Low levels in the Herth Hope scale have been reported in people with MCS (Gibson, 1999).
Illness belief system	Suggests that chemically sensitive patient beliefs about the nature of their illness are reinforced by treating physicians to the extent that symptoms become clinical. A study of a group of tunnel workers exposed to petrol contaminated soil suggests that chemical sensitivity can occur in naïve and non-litigious individuals (Davidoff et al., 1998). The possibility of an illness belief system in medical practitioners who cannot assist the patient also needs examination.
Immunological	Changes in immunological measures are sometimes found in MCS sufferers, but these are often not clinically significant and are not consistent in all MCS sufferers (Mitchell et al., 2000). The changes are also sometimes linked to post viral episodes, such as viral infections.
Impairment of biochemical pathways involved in energy production	Suggests that the fatigue seen in MCS (and CFS) sufferers may be due to impairment of basal energy metabolism in all cells. Those body systems with high-energy demands (such as muscles and the nervous system) are affected first.
Impairment of neurochemical pathways	Fatigue syndromes may be secondary to the altered sensitivity of the GABA receptor, an important neurological neurotransmitter (Corrigan et al., 1994).

Table 2 (*Continued*)

Mechanism	Comment
Limbic kindling	Limbic kindling is implicated in a range of conditions, including epilepsy (Loscher and Ebert, 1996), psychotic behaviour (Pontius, 1996), and drug abuse (Davis, 1996). For the chemically sensitive person, a chemical exposure (detected by the brain, but not the mind) causes the limbic system to impose a change in the way the brain is behaving. If there are also somatic (body) symptoms such as headaches from exposure to fumes, or respiratory or eye irritation, these are likely to become more exaggerated. Further, limbic kindling explains why low level chemical stimuli that do not initially produce a response eventually produce strong responses. That is, over time, normal behaviour produced by the brain is slowly over-ridden by limbic system activity. This theory is used to explain the development of rage in emergency services personnel after experiencing a critical incident and can be used to explain phobic behaviour in chemical sensitivity (Friedman, 1994). This theory may also explain the multi-organ nature of MCS, and time dependent increases in sensitivity (Bell et al., 1992). Limbic kindling also seems to be more strongly associated with olfaction (the smell of chemicals) than other stimuli (such as noise (Bell et al., 1995; Browne-DeGagne and McGlone, 1999)).
Malingering	Symptoms of MCS are produced so that sufferers can get out of work or receive compensation. This is most unlikely—the range of symptoms between sufferers is too consistent to be based on random symptoms used by many individuals for the purposive avoidance of work (McSherry, 1993).
Neural sensitisation	This is the progressive amplification of a response from repeated intermittent exposures to chemicals (Bell et al., 1998). The mechanism is thought to be a two stage process of initiation (activation) and sensitisation (Arnetz, 1999). Development of an animal model for MCS has provided some support for the sensitisation hypothesis (Sorg, 1999).
Neurogenic inflammation (in upper respiratory tract infection)	It is known that respiratory tract infections produce biochemicals (such as cytokines and messenger peptides) which can cause sensitisation of nervous cells located in the respiratory system. Suggests a possible mechanism of site specific nervous system sensitisation.
Olfactory threshold sensitivity	Suggests that MCS sufferers have increased olfactory thresholds. The evidence for this effect is equivocal. One study suggests changes in neurophysiological function in MCS sufferers following exposure to odourants (Callender et al., 1994), while another is not supported by experimental trials with MCS patients and matched controls (Doty, 1994). However, electroencephalography studies in normal subjects suggest that low intensity odour exposures are associated with changes in brain wave activity before conscious awareness of the odour (Schwartz et al., 1994). This study also shows that cacosmic subjects had greater effects.
Overload of biotransformation pathways (also linked with free radical production)	The functional reserves in biotransformation capacity vary from individual to individual. If this reserve is close to saturation or if it is depleted, the body will not be able to deal with further toxic exposures. Most MCS sufferers have some disruption in biotransformation processes (although not usually observed using the crude measures used clinically, for example, in liver disease). Also supports concepts of increasing sensitivity to lower concentrations and increasing numbers of chemicals. For example, a suggestion of impaired sulphation pathways in biotransformation has been reported (McFadden, 1996).
Panic disorder	The smell of chemicals may produce odour mediated panic attacks (Dager et al., 1987).

Table 2 (*Continued*)

Mechanism	Comment
Psychological or psychiatric illness	Suggests that MCS is produced as a by-product of misdiagnosed psychological or psychiatric illness. Obviously, the possibility of psychological disease should be excluded in diagnosis of MCS. There is little credible data that affected individuals show signs of psychopathology that: (i) preceded the exposure period; (ii) exceed those expected for a comparable medical condition; (iii) are consistent in different sub-groups (male/female, young/old, newly/chronically ill); and (iv) symptoms of MCS reduce when psychopathological symptoms are modified (Davidoff, 1992a). Support for treatment approaches that use avoidance regimens is available, whereas behavioural conditioning approaches do not appear to work (Simon, 1994).
Psychosomatic condition	Suggests that symptoms are of physiological or psychological origin (Davidoff, 1992b). This is unlikely as most symptoms are related to the conventional toxicity of the chemicals, but at a much lower concentration. Also, the symptoms of MCS sufferers are not entirely overcome by psychological interventions (Miller, 1994).
Sensitisation of the neurological system	"Neurogenic switching" occurs where a stimulus at one site can produce a reaction at another site (Meggs, 1995b).
Somatic depressive symptomatology	MCS is often associated with depression, with content overlap with somatic complaints (Browne-DeGagne et al., 1998).
Time dependent sensitisation	Refers to the ability of mild stresses, whether pharmacological or environmental, to induce physiological and behavioural effects which then progress as a function of time since exposure. The sensitisation is stronger on later exposures (Antelman, 1994).
Toxicant induced loss of tolerance (TILT)	A two stage process of chemicals that (1) initiate a loss of tolerance to chemical exposures (abdication as opposed to addiction) and (2) precipitate multisystem symptoms (Miller, 1999).

possible mechanism for MCS (Graveling et al., 1999).

2.3. Exposures that precipitate symptoms of MCS

Initially, individuals respond to one sort of chemical exposure, but if the spreading or broadening phenomenon occurs, the affected individual may respond to a much wider range of chemicals, and the exposures that precipitate symptoms become lower and lower. Table 3 (based on Meggs, 1992; Miller and Ashford, 2001 and personal experience) shows a wide range of exposures that have been reported to provoke such symptoms in the chemically sensitive individual.

Evidence suggests that most initiating symptoms are not from heavy exposures. Rather, exposure backgrounds with low levels of chemical exposure appear, paradoxically, to be more likely to be associated with MCS than do high exposure settings (Cullen et al., 1992).

2.4. Chronic fatigue in MCS

Chronic fatigue is a common outcome, but that debilitating fatigue and a number of associated symptoms following a viral infection for periods greater than 6 months has been given the name post viral chronic fatigue syndrome. People exposed to chemicals may also report similar types

Table 3
Incitant exposures implicated in chemically sensitive individuals

Type of exposure	Precipitating exposure	
Specific chemicals	Ammonia	Mineral turpentine
	Bleach	Petrol
	Formaldehyde	Toluene
	Glutaraldehyde	White spirits
Workplace contaminants	Adhesives	Soldering fumes
	Industrial air contaminants	Solvents
	Pesticides in building fumigation	Sulphur residues and processing fumes
	Photocopy toner	Utility gas
	Smoke	Vapours from paints
Domestic contaminants	Bed linen washed with detergents, or treated with starch	New carpets
	Chloride in water	New clothes
	Cleaning products, disinfectants, bleach	Newspapers and magazines
	Cosmetics	Off-gases from some construction materials
	Food additives/contaminants, flavouring agents, preservatives, and sweetening agents	Plants (different types)
	Fragrances from perfumes and toiletries	Plastic containers
	Insect sprays and repellents	Synthetic textiles
	Laser printer and photocopier emissions	Synthetic vitamins
	Medication and drugs, including antibiotics, sulphonamides, aspirin	Tar fumes (from roads and roof tar)
	New cars	Tobacco smoke (including passive smoking)
		Trees (different types)
		Vehicle exhausts (petrol and diesel)
		Water contaminants

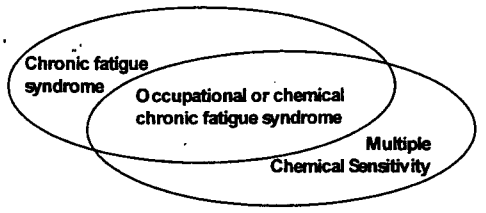

Fig. 2. The relationship of chronic fatigue syndrome and MCS.

of symptoms (but with more symptoms and probably less fatigue (Winder, 1994)). Fatigue, and chronic fatigue, is often part of MCS.

However, both these descriptions relate to a condition where the normal body mechanisms for dealing with exposure (either to a virus or chemicals) do not work properly, and getting well takes much longer than it would ordinarily (in some cases more than 2 years, if at all (Miller, 1996)). Indeed, as noted above, some of the features of MCS have similarities with chronic fatigue syndrome, such as fatigue, hypersensitivity and depression. It is possible to consider that these particular syndromes are at two ends of a continuum.

The chemically exposed individual with debilitating fatigue may not meet all the diagnostic criteria of chronic fatigue syndrome or MCS. In some cases, they may be closer to one than the other. This makes diagnosis (see Fig. 2) and treatment problematic.

However, chemically (or workplace) related chronic fatigue, that is the presence of fatigue and other symptoms following chemical or workplace exposures, sits between these two descriptions.

2.5. The phenomenon of "spreading"

Often the sensitivity to one exposure spreads to a wider range of agents. This "spreading" or "broadening" phenomenon is fairly characteristic of MCS, but causes problems for some treating medical practitioners, who find it difficult to believe that such a wide range of exceptionally low level exposures can induce such a wide variety of symptoms in many organ symptoms. Most diseases have a much narrower spectrum of symptoms and signs, so MCS does not fit into the pattern of illnesses with which medical practitioners are familiar. In many cases, diagnostic tests are not helpful in assisting diagnosis (Kehrl, 1997; Bartenstein et al., 1999).

2.6. Phases of MCS

There are three distinct phases of MCS:

- initial signs and symptoms to low level exposure to chemicals which recede with avoidance of exposure;
- reversible sensitivity, with intensifying signs and symptoms after continuing exposure, but partial or total reversal of symptoms after recognition of the condition and avoidance of exposure; and
- permanent MCS, after substantial or intense exposure, escalation of symptoms (sometimes, but not always with clinical correlates) and spreading of effects to other chemical exposures.

The stage of the condition that any person progresses to is invariably a matter of appropriate diligence by MCS sufferers, their medical advisers and sometimes, their employers.

2.7. MCS and compensation

Although the basis of MCS is debated in medical circles, it has achieved credibility in workers' compensation claims in the USA, in liability case law and in interpretation of regulations by various US Federal Government Departments (Gots, 1995). The first cases of payment of disability benefits to patients with MCS occurred in Hawaii in 1979, Oregon in 1986, California in 1987, Minnesota in 1990 and Pennsylvania in 1990 (Hilleman, 1991). Since the early 1990s, other cases in many US states have been successful.

There have been a number of cases of medical retirement or compensation for chemical sensitivity in Australia over the past few years, and judgements are now available in Australia regarding cases involving MCS (His Honour Judge Neilson, 1997; The Honourable Justice Campbell, 1988).

3. Conclusions

There are an increasing number of people showing unspecific symptoms related to low level occupational (or sometimes environmental) chemical exposures.

With regard to the links between exposure and adverse effect, the body has a substantial number of mechanisms that allow re-establishment of normal function after disruption or dysfunction. Exposure to toxic chemicals may cause a disruption in normal function, which in turn may activate individual defence mechanisms (depending on the type of effect). The process of activation depends on:

- the amount of toxicant absorbed. This includes both the specific toxicant causing the adverse effect, and any pre-existing toxicant(s) from previous exposures;
- the condition of the normal functions and processes of the body;
- status of pre-existing body defence mechanisms, capabilities and functional reserves; and
- in some cases, individual susceptibility.

While there is usually a process of chemical injury based on a sequence of molecular, functional and pathological changes, some molecular or functional alterations may be as toxicologically significant as the pathological changes they cause. These should not be ignored in the absence of measurable pathology, injury or disease.

With regard to dosimetry, toxicity at the low end of a dose–response relationship is improbable, but not impossible. A case of toxicity may arise a sufficiently large enough population that can be positioned on a long asymptotic curve approaching zero. Therefore, no new theory is required to explain the phenomena of low level toxicity—the dose–response relationship still applies.

With regard to the role of multiple exposures, and the interactions that multiple exposures may have with each other remains an important, if still largely unanswered question. A fuller understanding of the role of additive, potentiative and synergistic interactions in the development of low dose toxicity remains critical.

With regard to the mechanisms of low dose toxicology, and more specifically, MCS, a range of models has been proposed to explain these phenomena, including the immunological, neuropsychological, toxicological and sociological models. None work adequately in isolation, and the medical or scientific explanation of polysymptomalogy is yet to be established, although working definitions, and a diagnostic label (MCS) have been defined.

However, when a low level chemical effects occur, the question that should be answered is not "does this effect correspond with identifiable medical conditions or pathological correlates?" or "why does no-one else seem to be affected by what do not appear to be high levels of exposure?" but more "would the symptoms have occurred if the person had not been exposed?" Subjects with the chemical exposures that precipitate symptoms of MCS suffer from a syndrome of disability from which they may never recover from adequately and, because of a temporal relationship between exposure and effect, are legitimate cases to consider as being chemically associated.

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